Ideopathic sudden sensorineural hearing loss

Stokroos, Robert Jan

IDIOPATHIC *SUDDEN* SENSORINEURAL HEARING LOSS

ROBERT STOKROOS

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Stellingen behorende bij het proefschrift:

Idiopathic Sudden Sensorineural Hearing Loss

1. ISSHL: een moeilijke oor-zaak.

2. Zowel het vóórkomen als de gevolgen van ISSHL worden onderschat.

3. Op macroniveau wordt de prognose van ISSHL gunstig beïnvloed door het structureel toepassen van de stemvork bij ooronderzoek in de eerste lijn.

4. ISSHL is behalve een otological emergency ook een radiological emergency.

5. Een virale labyrinthitis lijkt een belangrijke rol te spelen in de pathofysiologie van ISSHL.

6. Het is moeilijk om een goed oordeel te geven over een onderwerp waarover iedereen al een mening heeft.

7. Het uitvoeren van multicentre clinical trials wordt bemoeilijkt door de noodzaak om het onderzoeksprotocol in ieder centrum door een medisch ethische commissie te laten beoordelen. Ook de daarvoor geëiste beoordelingsvergoeding moet ter discussie worden gesteld.

8. Verhalen over het verwijderen van het nervus vestibularis schwannoom en over de opbrengst van een dagje vissen lijken vaak op elkaar: bij beide wordt op den duur de centimeter korter dan hij was.

9. In een tijd waarin het uitdragen van medisch technische hoogstandjes regel is en ziekenhuizen als een kathedraal het stadsbeeld markeren wordt de maakbaarheid van gezondheid en welbevinden gemakkelijk overschat.

10. Opkomst en neergang van "Reality TV" zijn intrinsiek aan de verzorgingsstaat.

11. Het veiligheidsideaal, zoals wordt gesuggereerd door het inbouwen van steeds meer airbags in auto's wordt pas bereikt als het aangereden automobiel vanzelf ter recycling zweeft.

12. Shakespeare waarschuwde al voor de toxiciteit van oordruppels.
(Hamlet I.v.65-82, N Engl J Med. 1982; 307: 259-61/1531)

13. Prosper Menière: zelfs over de spelling van zijn naam bestaat geen consensus.
(Laryng Rhinol Otol. 1984; 63: 381-5)

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voor Rosina,
aan mijn ouders.

CONTENTS

Chapter 1

INTRODUCTION

Introduction

Hearing is a primary prerequisite for interaction with our environment. Loss of hearing strikes in the very core of our existence. In sudden hearing loss, its abruptness makes eventual acceptance even more difficult. The sensorineural nature of the hearing loss seriously limits potential therapeutic options, in contrast to a conductive hearing loss. For a small minority of sudden sensorineural hearing losses an identifiable cause exists, in some cases giving a therapeutic directive. The idiopathic character of the sudden sensorineural hearing loss discussed in this thesis comprises the majority of sudden sensorineural hearing losses and does not reveal directives towards its etiology or treatment. Due to its enigmatic etiology and its disappointing treatment results, Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) is confronting the clinician with an intricate problem.
Only in the context of history some relief can be found: the sense of hearing has been puzzling physicians throughout the past millennia[1,2]. The earliest medical writing is to be found in Egyptian papyri, the most famous of which is the Papyrus Ebers, sold by the citizens of Luxor to Professor Georg Ebers of Leipzig in 1872. It has been written about 1550 BC and consists of lists of empiric remedies. One of the prescriptions is for deafness:

> *"For an ear that hears badly - red lead, and resin from the am-tree, grind to powder, rub in fresh olive oil and apply to the ear".*

The school of Salerno, being the first medical school in Europe, was at its heydays during the great crusades (1096-1270). Its "Regimen Sanitatis Salernitanum" summarizes probably one of the earliest differential diagnoses of sudden hearing loss:

> *Our hearing is a choice and dainty sense,*
> *And hard to mend, yet soon it may be marred.*
> *These are the things that breed it most offence*
> *To sleep on stomach full, and drinking hard:*
> *Blows, falls and noise, and fasting, violence,*
> *Great heat, and sudden cooling afterward:*
> *All these, as is by sundry proofs appearing,*
> *Breed tingling in the ears and hurt out hearing.*

Otological history did not pass by Groningen completely. The first textbook of otology "De Auditus Instrumento" was written in 1572 by Volcher Coiter (1534-1600), who originated from Groningen. He summarized his knowledge regarding the physiology of hearing as follows:

> *"The main function of the tympanic membrane is to protect the middle ear and to preserve the purity of the 'Aer Implantatus', which conducts sound to the cochlea. This cavity also contains air and acts like a resonator, increasing the sound, which then impinges on the ramifications of the auditory nerves".*

The term 'Aer Implantatus' originates from an ancient belief that this air was implanted by the Maker, but according to Coiter, it originated in the external ear and was filtered and warmed in the mastoid cells.
One of the first descriptions of sudden sensorineural hearing loss can be ascribed to Prosper Menière (1799-1862), thereby adding another controversy to his famous case history. Menière reported to the Academy of Medicine in Paris on January 8th, 1861 as follows:

> *"I have spoken elsewhere, a long time ago, of a girl who - journeying on the box-seat of a stage coach - became as a result of the severe cold suddenly and completely deaf".*

The case was subsequently published in the Gazette Médicale de Paris on September 21st, 1861.
In our era, publications regarding sudden hearing loss have multiplied. In 1922, Kobrak[3] described a case of sudden hearing loss for which no explanation could be given. In 1933, Colett[4] reported to the Third Congress of the Societas Oto-Rhino-Laryngologica Latina, and put forward "serous meningitis" to be responsible for the hearing loss. In 1944, De Kleijn[5] proposed a vascular incident to cause sudden sensorineural hearing loss. In 1957, Bierman defended his thesis entitled "Sudden Perceptive Deafness" in Leiden, appreciating a viral role in the pathogenesis of ISSHL[6]. Since then, considerable efforts have been made by various authors to unravel the pathophysiology of ISSHL. Today, the etiology of ISSHL has not been elucidated and no truly successful therapeutic regimen exists.
ISSHL is probably resisting these efforts because the two approaches often applied in medical science are bound to fail in ISSHL[7]: empirical control of its therapy is hindered by its low incidence, and although the logical approach has elicited divergent hypotheses on its pathophysiology, these are hard to verify in the delicate, closed compartment formed by the inner ear.
Thus, modesty seems obligatory when attempting to stretch these limitations which are implicit to medical science itself. In ISSHL, determination in establishing its pathophysiology and therapy is justifiable because every ENT-surgeon is confronted at a regular interval with patients who have, for no apparent reason, suddenly lost their hearing. They demand a proper explanation and are disappointed, as we are, by treatment results.
Any enigmatic disease has been subject to speculation on its pathophysiology and the panacea for ISSHL has been abandoned as often as it has been presented.
In this thesis, a meta-analysis of recent literature is performed on etiology and treatment of ISSHL. Etiological, diagnostic and therapeutical issues are investigated by an epidemiological survey among Dutch and Flemish ENT-surgeons. Based on these results a hypothesis concerning etiology and treatment of ISSHL is deduced and subsequently tested in an animal model. The implications of this hypothesis are verified in clinical practice. The two main limitations of ISSHL research mentioned previously are encountered as follows: insight in labyrinthine pathology of ISSHL

without disturbing the integrity of the inner ear might be provided by using modern MRI techniques. By using a multi-center study design, with the collaboration of many ENT-surgeons, incidence problems might be solved.

Outline of the thesis

Current hypotheses regarding the etiology of ISSHL with their supportive findings are reviewed in Chapter 2. Accumulating circumstantial evidence implies a subclinical viral labyrinthitis in explaining a majority of ISSHL cases. This hypothesis is assessed further in this thesis.
Divergent therapeutic strategies have been applied in ISSHL. These are reviewed in Chapter 3. Considerable difficulties arise when evaluating therapy of ISSHL. Among them its inconsistent definition, its tendency to recover spontaneously and its low incidence. These impede validation of many therapeutic strategies in ISSHL.
Research efforts are warranted by their applicability in daily practice. From a survey on ISSHL in the Netherlands and Flanders, an inventory of diagnostic and therapeutic strategies in ISSHL is made and some epidemiological estimates can be derived. These are reported in Chapter 4.
In Chapter 5, an effort to gain further insight in the pathogenesis of ISSHL by using an animal model is described. Experimental herpes simplex viral labyrinthitis is elicited in the guinea pig and cochlear function and cochlear structure are evaluated.
In Chapter 6, the influence of treatment on this animal model is assessed, using prednisolone and the antiviral drug aciclovir (Zovirax®), both as a monotherapy and as a combination therapy.
The application of modern imaging techniques might reveal labyrinthine pathology in ISSHL. Thirty-six patients suffering ISSHL were studied by Magnetic Resonance Imaging. Our findings are discussed in Chapter 7.
The verification of the therapeutic value of the combined treatment with antiviral and anti-inflammatory therapy in ISSHL patients required the combined effort of many Dutch and Flemish ENT-surgeons and their patients. In Chapter 8 the results of a prospective multicenter clinical trial regarding antiviral and anti-inflammatory therapy of ISSHL are reported.
In Chapter 9, the results of the study are summarized and future prospectives with regard to further investigations are discussed.

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Chapter 2

THE ETIOLOGY OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS: *a review of the literature*

Stokroos RJ, Albers FWJ. The etiology of idiopathic sudden sensorineural hearing loss: a review of the literature. Acta ORL Belg 1996; 50: 69-76.

Introduction

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) is a shocking event to the patient and a puzzling condition to the clinician, because its etiology has not been elucidated yet and therefore treatment is empirical. This review was designed to evaluate reports concerning the etiology of ISSHL critically. The implications of the results with regard to the pathophysiology of ISSHL and the possibilities for future research are discussed.
No consensus exists in literature on the definition of ISSHL. In order to conduct an adequate review on the etiology of ISSHL we used the following definition:

Inclusion criteria:
1. Sensorineural hearing impairment of unknown etiology.
2. Hearing impairment occurring within 24 hours.
3. Hearing impairment is nonfluctuating.
4. Hearing impairment averages at least 30 dB HL for three subsequent one octave steps in frequency in the standard pure-tone audiogram.

Exclusion criteria:
1. Identification of specific causes of sensorineural hearing impairment using common clinical, laboratory and radiological investigations.
2. A history of fluctuating hearing impairment.
3. A compromised otological history.

The symptomatology and natural course of ISSHL approximating our definition has been described by Mattox and Simmons[1]. They described ISSHL in 89 ears of 88 patients. Mean age was 46 years, varying from 10 to 79 years. Hearing impairment most often developed in a few hours, some hearing losses were present at awakening. Many patients complained about fullness or pain in the ear. Tinnitus was frequently noticed afterwards, but in some cases it preceded the hearing loss. Some patients experienced postural instability or vertigo. Spontaneous recovery to a functional hearing level was found in 65% of cases. Prognosis was related to the severity of the initial hearing loss and vestibular involvement. Prognosis also seemed to be related to audiogram contour. Downsloping audiograms indicating pathology in the base of the cochlea were associated with a less favourable prognosis compared to upsloping audiograms, indicating damage to the apex of the cochlea. Therefore, it was concluded that recovery was better at the apex than at the base of the cochlea.
The four most commonly encountered hypotheses trying to explain Idiopathic Sudden Sensorineural Hearing Loss are:

a. Impairment of labyrinthine blood supply,
b. Inner ear membrane ruptures,
c. Viral infection of the labyrinth,
d. Autoimmune mediated cochlear malfunction.

Combinations of these hypotheses have been postulated as a possible cause of ISSHL in the literature.

Review

We selected a combination of clinical and experimental characteristics commonly used as evidence for a certain etiology of ISSHL. The literature was reviewed using the following characteristics:

a. Clinical findings,
b. Laboratory,
c. Radiology,
d. Post mortem temporal bone histopathology,
e. Experimental evidence.

Studies listed in table 1 were included since the definition of ISSHL essentially approximated our inclusion and exclusion criteria. These studies contained a well-documented patient group and/or a clear experimental design.

Table 1: Characteristics versus possible etiology of ISSHL as described in the literature

	Vascular impairment	**Membrane rupture**	**Viral infection**	**Autoimmune mediated**
Clinical evidence	Kitamura[2] Plasse[3] Escarcega[4] Ogawa[5] Sando[6] Schuknecht[7] Yabe[8]	Nomura[16] Simmons[17] Gussen[18]	Van Dishoeck[23] Kobayashi[24] Pyykko[26] Okamoto[27] Mattox[1]	McCabe[43] Kanzaki[44]
Laboratory	Einer[9]		Veltri[29] Rowson[30] Wilson[31,32]	Elies[45] Veldman[46]
Radiology	Albers[10]		Albers[10]	
Histopathology	Belal[11] Yoon[12]		Schuknecht[33,34,35] Yoon[36] Sando[37] Fukuda[38]	
Experimental evidence	Igarashi[13] Perlman[14] Suga[15]	Simmons[19] Axelsson[20] Oshiro[21] Gyo[22]	Rarey[39] Nomura[40] Hirai[41] Fukuda[42]	Yamanobe[47]

Vascular impairment

clinical evidence

Kitamura and Berreby[2] described a patient suffering from sudden hearing loss of his right ear, with simultaneous development of hemiparesis and cranial nerve paralysis. Autopsy, performed 17 days later, showed severe arteriosclerosis, thrombosis of right basilar and vertebral arteries, and severe degeneration of the cochleovestibular cellular structures.

Plasse et al.[3] described unilateral sudden hearing loss postoperatively in 7 of 7000 patients who underwent cardiopulmonary bypass surgery. Cervantes Escarcega[4] described unilateral sudden hearing loss in 11 of 5975 patients who underwent open heart surgery. Both authors hold microemboli responsible for the hearing losses.

Ogawa and Kanzaki[5] reported 3 patients suffering from aplastic anaemia, developing sudden hearing loss just prior to, or at the onset of thrombocytopenia. It is speculated that inner ear haemorrhage is responsible for the sudden hearing loss in these cases. Sudden hearing loss has also been reported in leukemia by Sando and Egami[6], Schuknecht et al.[7] and Yabe et al.[8] On post mortem analysis, haemorrhage, after a period of 30 days followed by fibrosis and ossification was found in these inner ears.

laboratory

Einer et al.[9] performed a prospective evaluation of pathological haemostatic mechanisms in sudden hearing loss in 32 consecutive patients with sudden hearing loss. Twenty-eight healthy individuals functioned as a control group. They observed non-significant isolated aberrations in the haemostatic pathway, considered too discrete to be relevant for a causal role in sudden hearing loss.

radiology

Albers et al.[10] examined 5 patients suffering ISSHL using a combination of high resolution computed tomography and special magnetic resonance imaging techniques. By three-dimensional constructive interference in steady state magnetic resonance imaging (3 DFT-CISS MRI) excellent visualization of the membranous labyrinth was obtained. No fibrous or osseous obliteration of the intralabyrinthine fluid spaces was observed in any of the investigated temporal bones. This obliteration was expected if impairment of labyrinthine blood supply would have led to ISSHL.

temporal bone histopathology

Belal[11] described temporal bone histology of seven patients who underwent removal of an acoustic neuroma, in which the internal auditory artery was ligated. An autopsy was performed varying from one day to eleven years postoperatively. Severe cochlear degeneration was found, progressing to complete ossification of the cochlea one year after surgery. Yoon et al.[12] reported fibrosis and new bone formation in two cases in which sudden hearing loss was associated with vascular insult.

experimental evidence

Experimental efforts to prove a vascular etiology have been done by Igarashi et al.[13], Perlman et al.[14] and Suga et al.[15].

Igarashi[13] produced microembolization of the cochlea in dogs. This caused functional and histopathological damage to the cochlea, resulting in fibrous connective tissue proliferation, followed four months later by ossification of the cochlea. Perlman[14] surgically induced both arterial and venous occlusion of the guinea pig cochlea. Soon afterwards, extensive cochlear cellular destruction was observed, followed after one week by fibrosis and later by ossification of the cochlea. Suga[15] induced microembolization of the cochlea in guinea pigs by injecting a significant amount of barium sulfate into the vertebral artery. He sometimes found the blood flow to recover, but the cochlear potential disappeared without recovery. Adding vasodilators did not change these findings. Short term histological examination of the cochlea showed mainly barium sulfate particles, but after a few weeks atrophy, fibrosis and ossification was seen in the cochlea.

Membrane ruptures

clinical evidence

Direct or indirect trauma to the inner ear membranes can lead to a perilymph fistula. Nomura[16] ascribed spontaneous perilymph fistulas to inadequate control mechanisms of cerebrospinal fluid pressure fluctuations when performing activities such as nose blowing or physical exercise. The perilymph fistula results in dizziness or disequilibrium and hearing loss. If the fistula does not close spontaneously, exploratory tympanotomy should be performed.

Simmons[17] postulated inner ear membrane breaks as a possible cause of ISSHL. He explained sudden hearing loss over a broad frequency range by mixing of endo- and perilymph through a rupture of Reissner's membrane. Upon healing of this rupture, ionic equilibrium was reinstalled and hearing recovered. A small dip in the audiogram located the supposed membrane rupture. The inner ear membrane rupture was associated with a perilymph fistula to the middle ear. This hypothesis was supported by three case reports. Only the first case report slightly approximated our definition of ISSHL, the other two patients did not suffer idiopathic hearing losses but barotraumata. In all three cases a perilymph fistula was patched. No temporal bone histology was presented to support this hypothesis. Gussen[18] described two patients possibly having a double membrane break, but these cases did not match our definition of ISSHL.

experimental evidence

Experimental evidence suggests that perilymph leakage as a result from round or oval window rupture alone does not cause profound hearing loss[19,20].

Oshiro et al.[21] reported that the total hearing loss caused by simultaneous rupture of Reissner's membrane and the round window was larger than the sum of those caused separately.

Gyo and coworkers[22] found that simultaneous rupture of Reissner's membrane in the second turn of the cochlea and the round window in guinea pigs showed a larger increase in action potential threshold than did the control ears with only round window rupture. This threshold shift was not observed when Reissner's membrane was ruptured at other turns.

Viral infection

clinical evidence

Van Dishoeck[23] reported a preceding respiratory infection in 30-40% of patients with ISSHL and suggested viral infection as a possible cause of ISSHL. Mattox and Simmons[1] described the natural history of ISSHL in 88 patients. Twenty-eight percent had a history of an upper respiratory infection within one month before ISSHL occurred. Infections by several viruses such as mumps, measles, rubella, and herpes are known causes of acute sensorineural hearing loss[24,25]. Pyykko et al.[26] identified human Spumaretrovirus as a possible cause of ISSHL. These infections, causing acute sensorineural hearing loss may sometimes follow an otherwise asymptomatic clinical course[27]. Liao et al.[28] described similarities in the recovery of hearing loss induced by Lassa virus and recovery of ISSHL.

laboratory

Veltri et al.[29] surveyed 77 patients with ISSHL and found seroconversion in 65% (49/77). Multiple agents were involved in 24 of 49 cases. Rowson et al.[30] and Wilson et al.[31] reported similar findings.

Wilson[32] observed herpes seroconversion in association with sudden hearing loss. The herpes seroconversion often occurred in association with other viral titer changes.

radiology

Albers et al.[10] examined 5 patients suffering ISSHL using a combination of high resolution computed tomography and special magnetic resonance imaging techniques. The results of this study support a viral pathogenesis of ISSHL.

temporal bone histopathology

Schuknecht et al.[33,34,35] presented temporal bone histology of 12 patients having suffered from ISSHL. In 6 of these patients viral upper respiratory infection coexisted. Atrophy of the organ of Corti and tectorial membrane, more outspoken in the basal coil and diminishing towards the apex was the most striking feature. The vestibular labyrinth and stria vascularis were less involved. No damage to vascular or neural structures was found. No fibrosis or ossification was found. No perilymph fistulas or signs of previous membrane breaks were seen. The contralateral (healthy) ears functioned as a matched control group. The authors found cochlear changes resembling those found after hearing loss associated with rubella or mumps. Yoon et al.[36] and Sando et al.[37] reported similar observations.

Fukuda and coworkers[38] postulated reactivation of latent viral infection of the spiral ganglion as a possible explanation for ISSHL. In five patients, without a history of recent herpes infection or ISSHL, herpes simplex virus type 1 DNA was found in all of 10 spiral ganglia in post mortem analysis using polymerase chain reaction. Newborn spiral ganglia were negative for HSV-1 DNA. The exact mechanism operational in the possible reactivation of latent viral infection remains obscure.

experimental evidence
Rarey et al.[39] inoculated ferrets with influenza viruses and induced conductive and/or sensorineural hearing losses.
Nomura et al.[40] inoculated guinea pig inner ears with herpes simplex virus. The histopathological characteristics were compared to the histopathological findings of the temporal bones of a woman who suffered sudden deafness 33 years before decease. Changes in experimentally induced herpes simplex virus labyrinthitis resembled those found in the human temporal bones after sudden deafness.
Hirai[41] inoculated guinea pigs with Sendai virus. Cochlear histopathology resembled descriptions of temporal bones in ISSHL. The resemblance of labyrinthine histopathology induced in animal experiments and temporal bone histopathology found in post mortem investigation of patients having suffered ISSHL has also been reported by Fukuda et al.[42]

Autoimmune labyrinthitis

clinical evidence
McCabe[43] described 8 cases of autoimmune sensorineural hearing loss. Kanzaki[44] interpreted these cases as patients suffering from atypical Cogan's syndrome or variants of polyarthritis nodosa.

laboratory
Elies and Plester[45] proposed an autoimmune pathogenesis for various inner ear diseases. They found a raised CSF total protein and positive tissue auto-antibodies in patients suffering from Menière's disease, sudden deafness and chronic progressive sensorineural hearing loss.
Veldman et al.[46] analyzed sera from 31 sudden deafness patients using Western Blot assays with heterologous swine inner ear antigen and protein extracts of other organs. In 65% of patients cross reacting antibodies were found, indicating an autoimmune origin.

experimental evidence
Yamanobe and Harris[47] tried to identify the spontaneous course of experimental autoimmune labyrinthitis induced in guinea pigs. They injected processed homogenized bovine temporal bones as "crude inner ear antigen" and measured hearing threshold shifts, which never completely recovered. Histology of the cochlea showed a lymphocyte and poly-morphonucleocyte cellular infiltration in the inner ear,

with some spiral ganglion cell degeneration, thus suggesting a possible role for the cellular immunity in inducing hearing loss.

Discussion and conclusions

Vascular impairment

A vascular etiology for ISSHL is attractive because its abrupt onset resembles other vascular catastrophes in the central nervous system. Sudden hearing loss is observed after cardiac surgery, in which microembolism in the cochlea is a probable but unproven pathogenesis. However, the described clinical cases do not fulfill entirely the proposed definition of ISSHL with regard to the pre-existing history of arteriosclerosis.
Experimentally induced hearing losses of vascular origin are predominantly irreversible. This is in contrast to ISSHL, where spontaneous recovery rates are reported between 45-65%[1,48]. Fibrosis and ossification of the cochlea, reported after experimentally produced impaired blood supply or by known infarction of the cochlea, were not found in post mortem temporal bone examination[10,14], or by imaging techniques, in patients with ISSHL[10].
A wide variation in age is found in ISSHL patients, not excluding childhood (Ullrich and Aurbach[49]). Often these patients have no evidence of chronic vascular disease and are otherwise healthy. No cardiovascular risk factors differentiating ISSHL patients from normal subjects could be identified (Schmolke et al.[50], Preyer et al.[51]).
In the literature, we find insufficient clinical and experimental evidence to hold a vascular cause responsible for idiopathic sudden sensorineural hearing loss.

Inner ear membrane ruptures

Rupture of inner ear membranes is an interesting hypothesis explaining the suddenness and spontaneous recovery found in ISSHL. Clinical evidence is limited to one case report, which refers to a perilymph fistula, which is not in accordance with the definition of idiopathic sudden sensorineural hearing loss.
Although severe hearing loss can be provoked experimentally by inducing double membrane breaks, the question remains if these breaks occur spontaneously in ISSHL. Temporal bone histology of well-documented ISSHL patients did not show evidence of (previous) membrane breaks. The inner ear membrane break hypothesis therefore lacks convincing clinical and histopathological evidence.

Viral infection

Viral upper respiratory infection is frequently reported in ISSHL patients, but also occurs often in the normal population. A viral etiology of ISSHL is supported by histopathological studies of the cochlea in ISSHL in which pathological changes

resemble those found in known labyrinthine viral infection and in experimentally induced viral infection. Imaging studies of the inner ear in ISSHL by Albers et al.[10] support these findings.
The presence of latent neurotropic herpes viruses in the spiral ganglia of asymptomatic individuals, and the rise in herpes titers together with seroconversions for other viruses in ISSHL makes reactivation of latent neurotropic viruses in the cochlea of ISSHL patients a most interesting hypothesis. After reviewing the literature we find this etiology worth to be investigated further.

Autoimmune labyrinthitis

Autoimmune labyrinthitis is sometimes proposed as an explanation of ISSHL, although evidence is sofar circumstantial. The main disadvantage of this theory is the inability to explain the suddenness of ISSHL in otherwise healthy individuals, instead of the relapses and remissions observed in the clinical course of autoimmune diseases. Patients suffering from ISSHL have no systemic manifestations of autoimmune disease. Temporal bone histopathology after experimentally produced autoimmune cochleitis does not resemble histology found after ISSHL. In the literature we found insufficient evidence to accept or reject autoimmune disease as a cause of ISSHL.

After reviewing the literature on the etiology of ISSHL we find impairment of vascularization and inner ear membrane ruptures not likely to play a major role in causing ISSHL, according to our proposed definition of ISSHL. We find insufficient evidence for an underlying autoimmune disease and therefore we acknowledge viral labyrinthine infection as being responsible for an important proportion of idiopathic sudden sensorineural hearing losses. This hypothesis needs further attention, not only in research but also in therapy of ISSHL.

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Chapter 3

THERAPY OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS: *a review of the literature*

Stokroos RJ, Albers FWJ. Therapy of idiopathic sudden sensorineural hearing loss: a review of the literature. Acta ORL Belg 1996; 50: 77-84.

Introduction

Treatment of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) is empirical, because the etiology of the hearing loss has not been elucidated yet. Many strategies for treatment of ISSHL have been proposed over the years. This reflects the lack of a convincing successful regimen[1]. Evaluating the success of a treatment modus is difficult because its performance has to be better than the high spontaneous recovery rate of ISSHL, reported between 45-65%[2,3]. In addition, studies containing sufficient patients are relatively scarce, due to the low incidence of ISSHL.
For an effective investigation of the various treatment modalities consensus on the definition of ISSHL is obligatory. In chapter 1[4] we proposed the following definition of ISSHL.

Inclusion criteria:
1. Sensorineural hearing impairment of unknown etiology.
2. Hearing impairment occurring within 24 hours.
3. Hearing impairment is nonfluctuating.
4. Hearing impairment averages at least 30 dB for three subsequent one octave steps in frequency in the standard pure-tone audiogram.

Exclusion criteria:
1. Specific causes of sensorineural hearing impairment which can be identified using common clinical, laboratory and radiological investigations.
2. A history of fluctuating hearing impairment.
3. A compromised otological history.

Most treatment protocols are based on one or more of the following strategies:

a. Optimizing cochlear blood supply,
b. Anti-inflammatory medication,
c. Miscellaneous treatment.

We reviewed the literature and evaluated whether one of the above strategies was effective in achieving hearing improvement in ISSHL according to our definition. The studies were analyzed with regard to the requirements of a clinical drug trial:

1. Comparativeness: the results obtained in the group of patients receiving the drug under study have to be compared to those obtained in a reference group of patients, for example receiving no therapy.
2. Internal validity: the methodology used should allow a good estimate of the therapy-bound effect[5]. The methods used to ensure internal validity are randomization, double-blinding and imply a prospective study design.
3. External validity: generalization of the results is possible by the strict definition of the disease according to the inclusion and exclusion criteria.

Review

I. Optimizing cochlear blood supply

A. Clinical studies (Table 1)

Kronenberg et al.[6] evaluated the ability of procain hydrochloride, a vasodilator, and dextran (Rheomacrodex®), a plasma expander decreasing blood viscosity, to achieve hearing improvement in ISSHL. They performed a prospective randomized double blind clinical study of 27 ISSHL patients. Thirteen patients received procain hydrochloride and dextran, 14 patients received placebo. No significant differences in hearing improvement were found between both groups. The definition of ISSHL in this study approximated ours, the study design fulfills our requirements concerning comparativeness, internal and external validity.

Kubo et al.[7] performed a prospective paired double blind clinical trial comparing two treatment regimes in 162 ISSHL patients. 80 patients received defibrinogenation-therapy with batroxobin (Defibrogenase®), a thrombinlike venom enzyme decreasing fibrinogen levels and thus reducing blood viscosity. 82 patients received betamethazone (Celestone®), a glucocorticosteroid. Hearing recovery was measured using a four point recovery scale. In the batroxobin treated group recovery was 57.3%. In the betamethasone treated group recovery was 38.7%. This difference was statistically significant.

Three years later, Shiraishi et al.[8] reported results of the same study again, now comparing absolute values for hearing threshold levels instead of the former used four point hearing recovery scale. The batroxobin treated group consisted of 82, the betamethazone treated group of 86 patients. In achieving hearing recovery, defibrinogenase therapy performed slightly better ($p < 0.1$) when evaluated two weeks after starting therapy, thus seemed to achieve faster recovery than betamethazone. When evaluated after finishing treatment, performance of both treatment modalities was comparable. The use of absolute hearing threshold levels instead of allocating patients to a four point recovery scale made differences between both treatment modalities less clear. In this study, the definition of ISSHL approximated ours, it meets our standards on internal validity but since no comparison to the spontaneous recovery rate of ISSHL was made, comparativeness is questionable.

Probst et al.[9] treated ISSHL with dextran and pentoxifillin (Trental®), increasing red cell deformity and thereby lowering blood viscosity. The study was designed as a placebo controlled, randomized, double blind clinical trial. Patients were divided in three groups; the first ($n = 67$) received a placebo, the second ($n = 53$) received pentoxyfillin only, the third ($n = 64$) received both dextran and pentoxifillin. Absolute hearing gains were compared. No significant differences in hearing gain were found between these treatment groups. The definition of ISSHL in this study approximated ours, the study design fulfills our requirements concerning comparativeness, internal and external validity.

Wissen and Aziz[10] treated 112 patients suffering from ISSHL. Treatment results were

evaluated retrospectively. Sixty-nine patients were treated with dextran and pentoxifillin. Twenty-seven were treated with dextran and the vasodilators nicotic acid and novocain. Sixteen were treated with nicotic acid and novocain. No significant differences in hearing improvement were found using these treatment modalities. ISSHL is not well defined in this study, and its design did not fulfill our criteria concerning comparativeness and internal validity.

Sudden hearing loss was treated with fibrinolysis using rt-PA (recombinant tissue-type plasminogen activator, Actilyse®) by Hagen[11]. Twelve patients suffering sudden hearing loss without vestibular symptoms were treated using rt-PA. In 7 patients, hearing was restored, in 3 patients some hearing improvement was obtained, two patients remained deaf. Based on this study, the authors do not recommend rt-PA as a treatment modality of ISSHL. Since the study lacked a control group, they find it difficult to distinguish between the therapy bound effect and the spontaneous recovery rate of ISSHL which can be expected slightly higher than average in this prognostically favourable patient selection. The study design did not fulfill our criteria concerning comparativeness and internal validity.

Wilkins, Mattox and Lyles[12] performed a retrospective evaluation of a "shotgun" regimen for sudden hearing loss, consisting of the diuretic dyazide, the vasodilator histamine phosphate, the glucocorticosteroid dexamethazone (Decadron®), the iodinated dye used in radiologic studies diatrizoate meglumine (Hypaque®), the vasodilator nicotic acid (Nicobid®), the plasma expander dextran and inhalations of a 5% carbogen / 95% oxygen gas mixture, supposed to improve cochlear blood flow. Hundred-twelve ears of 109 patients were evaluated. Thirty percent received the entire protocol, 70% received a varied part of the protocol. No significant difference in hearing recovery was found between these two groups. Of all patients, 26% achieved a complete recovery, 26-28% a partial recovery and 46-48% showed no response to treatment. The ability of each individual drug to produce hearing recovery was evaluated. No significant effects were found, except for diuretics, which caused a worse outcome in hearing recovery. A placebo treated or no treatment control group was not included in this study. The results fall within the range of spontaneous complete or good recovery reported in the literature when no treatment is given. In this design, we question comparativeness, internal and external validity.

Koehn and Nickol[13] treated 100 patients suffering sudden hearing loss with dextran, diazepam (Valium®) and vitamins A, B, C and E and added naftidrofuryl (Dusodril®) in half of the patients. Naftidrofuryl has antiserotinergic and therefore vasodilatory properties. No diagnostic criteria of ISSHL were given. Treatment results were analyzed retrospectively. Patients were divided in three age groups (under 30, 30-60 and over 60 years.) Naftidrofuryl treated patients achieved better hearing recovery in the middle aged group ($p < 0.01$). This study design did not meet our criteria on comparativeness, internal validity and external validity.

Laskawi et al.[14] performed a prospectively randomized clinical trial in 151 ISSHL patients, comparing naftidrofuryl and pentoxyfillin, both in combination with hydrocortisone and dextran. No difference between both treatment modalities was found. Since the study was not performed double blindly, we question internal

validity in this study design.
Hoffmann et al.[15] performed a prospective, randomized clinical trial in 80 ISSHL patients comparing the Ginkgo Biloba-extract EGb 761(Tebonin®) to naftidrofuryl. EGb 761 has vasoregulative activity, platelet activating factor antagonizing properties and it prevents membrane damage by inhibition of free radicals. After two weeks a borderline benefit ($p = 0.06$) of EGb 761 in relative hearing gain was found. The hearing gain was comparable to the hearing gain found when no therapy is established. No placebo treated control group is included, and the study was not performed double blindly. In this study design, we question comparativeness and internal validity.

Table 1: Treatment of ISSHL: Optimizing cochlear blood flow

Clinical study	Treatment
Kronenberg et al.[6]	procain/dextran vs placebo
Kubo et al.[7] Shirashi et al.[8]	baxtrobin v. bethamethasone
Probst et al.[9]	dextran/ pentoxifylline v. placebo
Wissen, Aziz[10]	dextran/ pentoxifillin v. dextran/ novocain/ nitotinic acid v. nicotinic acid/ novocain
Hagen[11]	rt-PA
Wilkins et al.[12]	histamine, dextran, diatriozate meglumine, carbogen, histamine, nicotic acid, diazide, dexamethazone.
Koehn, Nickol[13]	naftidrofuryl
Laskawi et al.[14]	naftidrofuryl v. pentoxyfillin
Hoffman et al.[15]	EGb 761 v. naftidrofuryl
Hultcranz et al.[16]	dextran, nicotinic acid, vitamin B
Bahgat, Shenoi[17]	O_2/ CO_2 inhalation
Fisch[18]	O_2/ CO_2 inhalation v. papaverine/ dextran

Hultcranz et al.[16] retrospectively evaluated the use of dextran, nicotinic acid and vitamin B in 80 ISSHL-patients. 32.5% of patients completely recovered, 35%

showed marked hearing improvement and 18.8 % moderate hearing improvement. Since no control group is included, establishing the therapy bound effect is impossible in this study. Treatment results approximate the spontaneous recovery rate in ISSHL. Based on this evaluation, the authors discontinued the use of this therapy modus in ISSHL. The study was not designed according to our criteria on comparativeness, internal and external validity.
Baghat and Shenoi[17] reported treatment of four well-documented cases of ISSHL with inhalation of a 5% CO_2 / 95% O_2 gas mixture, and found improvement of hearing in three cases. The study design did not fulfill our requirements concerning comparativeness, internal and external validity. Fisch[18] used carbogen inhalation in sudden deafness. In a prospective randomized clinical trial 46 patients suffering sudden deafness were treated either with inhalation of 95% O_2 and 5% CO_2 or with intravenous papaverine hydrochloride and dextran. Five days after treatment, no significant difference in hearing improvement was found between both groups. The study design did not entirely fulfill our requirements on comparativeness, internal and external validity.

B. Experimental studies (Table 2)
Nagahara et al.[19] have measured perilymph oxygen levels in inner ear hearing losses of various etiology. In sudden hearing loss they found low initial values of perilymph oxygenation and a normal rise in perilymph oxygenation in response to carbogen inhalation. Normal values were deduced from values obtained in two otosclerotic patients and in cats. Hearing was not influenced by the restoration of normal perilymphathic oxygenation.

Table 2: Treatment of ISSHL: Optimizing cochlear blood flow

Experimental study	Treatment
Nagahara et al.[19]	O_2 / CO_2 inhalation
Yagi et al. [20]	Angiotensin, papaverine, furosemid, pyridylcarbinol, naftidrofuryl, dextran, histamine, glycerol, $NaCO_2$
Pollock et al.[21]	O_2 / CO_2 inhalation
Prazma et al.[22]	O_2 / CO_2 inhalation

Yagi et al.[20] measured oxygenation of perilymph in cats in response to injection of vasoactive drugs. Of all drugs tested, only angiotensin induced a significant rise in perilymphathic pO_2. Papaverine hydrochloride, furosemid, pyridylcarbinol, naftidrofuryl and low molecular dextran did not alter perilymphathic pO_2; histamine,

50% glycerol and 7% Na_2CO_2 reduced perilymphathic pO_2.
Pollock et al.[21] demonstrated a rise in temporal bone blood flow in dogs, following inhalation of a CO_2 / O_2 gas mixture.
Prazma et al.[22] demonstrated a rise in endocochlear O_2, endocochlear potential and a slight decrease of cochlear microphonics in guinea pigs breathing a 10% CO_2 / 90% O_2 gas mixture.

II. Anti- inflammatory medication (Table 3)

In spite of their wide clinical use, few randomized prospective double blind clinical trials on the use of steroids in ISSHL are available. We encountered two studies in which the definition of ISSHL approximated our inclusion and exclusion criteria.
Wilson et al.[23] performed a double blind clinical trial including 67 ISSHL patients. Thirty-three received the steroids dexamethasone or methylprednisolone, 34 received a placebo. Fifty-two patients refused to participate and functioned as an untreated control group. After matching for age and vertigo, the steroid group achieved better hearing recovery than the placebo treated group and the untreated control group. This difference was significant ($p = 0.017$). Study design fulfilled our requirements concerning comparativeness, internal and external validity. The authors found viral infection of the cochlea most likely to cause of ISSHL and ascribe the beneficial effect of steroids to their anti-inflammatory action. However, patients presenting with a profound hearing loss remained refractory to therapy.
Moskowitz, Lee and Smith[24] performed a prospective clinical trial in 36 patients suffering ISSHL. Twenty-seven received dexamethazone, 9 received a placebo. Of the dexamethazone treated group, 89% recovered to functional hearing levels. Of the placebo group 44% recovered. This difference was statistically significant ($p < 0.01$). Study design fulfilled our requirements concerning comparativeness. The study was designed as a randomized prospective clinical trial, but double blinding is lacking, and therefore our requirements on internal validity are not entirely met.

Table 3: Treatment of ISSHL: Anti-inflammatory medication

Clinical study	Treatment
Wilson et al.[23]	dexamethazone/ methylprednisolone v. placebo v. untreated.
Moskowitz et al.[24]	dexamethazone v. placebo

III. Miscellaneous treatment (Table 4)

Numerous reports on various treatment strategies in ISSHL are available, including stellate ganglion block[25,26], multistep oxygen therapy[27], hyperbaric oxygen therapy[28], natrium-meglumine-diatrizoate (Urografin®)[29], diatrizoate meglumine (Hypaque®)[30] and xantinolnicotinate (Complamine®)[31], but no randomized double blind clinical trials are available to ascertain the therapeutic values of most of these strategies.
A few studies approximating our demands of comparativeness, internal and external validity are listed in table 4.
Use of the calcium antagonist nimodipin (Nimotop®) has been evaluated by Lenarz[32]. The primary therapeutic effect of calcium antagonists is the result of a vasodilatory and spasmolytic action on cerebral vessels. Secondly, a protective effect on hypoxic sensory cells is supposed, due to their property to lower intracellular calcium, thus lowering ATP use in these damaged cells. Eighty ISSHL patients were randomly assigned to two groups (n = 40), the first group receiving naftidrofluryl only, the second group also receiving nimodipine. No statistically significant difference between both groups was found. The definition of ISSHL used in this study did not entirely fulfill our inclusion and exclusion criteria. Although our demands on comparativeness, randomization and prospectiveness were met, double blinding is lacking, and therefore internal validity is questionable.
Meier et al.[33] evaluated treatment effectiveness of the calcium antagonist flunarizine (Sibelium®) in ISSHL in a non-randomized non-double blind prospective clinical trial. Thirty-seven patients received flunarizine, 67 placebo treated patients of a previous study[9] functioned as a control group. It was concluded that flunarizine did not improve recovery of sudden hearing loss. In this design, we question comparativeness, internal and external validity.

Table 4: Treatment of ISSHL: Miscellaneous treatment

Clinical study	Treatment
Lenarz[32]	nimodipin +/- naftidrofluryl
Meier et al.[33]	flunazerine v. placebo
Michel and Matthias[34]	taprosten v. mannitol

Michel and Matthias[34] performed a placebo-controlled double blind study on the treatment of ISSHL with the stable prostacyclin analog taprosten, assumed to have both vasodilatory and thrombocyte aggregation inhibiting properties. Twenty-two ISSHL patients were randomly assigned to taprosten or placebo treatment. Low-dose mannitol functioned as placebo. No statistically significant difference could be found

between both groups. The choice of placebo weakens comparativeness, internal and external validity in this study.

Discussion and conclusions

In ISSHL, therapy based on improving cochlear blood supply has been used extensively, although the use of plasma expanders and vasodilators lacks both experimental and clinical support. A beneficial effect of defibrinogenase therapy cannot be established, and a "shotgun" therapy for ISSHL only causes adverse effects. Studies on the use of naftidrofuryl lack proper design and thorough evaluation. Inhalation of CO_2/O_2 , although well evaluated experimentally, has not proven to be of clinical use.

In the literature, we found two well-designed studies supporting the beneficial effect of steroids in achieving hearing recovery in ISSHL, although the level to which hearing recovery is achieved is disappointing.

Reports on miscellaneous treatment modalities are numerous. Only a few studies meet our requirements concerning study design. In three well-designed studies the effect of two calcium antagonists and a prostracyclin analog was evaluated. No beneficial effect on achieving hearing improvement could be demonstrated.

In conclusion, no truly successful treatment modality in ISSHL exists. Application of steroids has a modest beneficial effect on hearing recovery.

In an extensive review of the literature, the etiology of ISSHL according to our definition is critically judged on clinical and experimental evidence[4]. A viral labyrinthine infection is regarded to be responsible for a large proportion of ISSHL. The beneficial effect of steroid therapy can be explained by its anti-inflammatory action, as described in earlier reports.

A viral pathogenesis of ISSHL deserves further attention in experimental research and therapy. Therefore, we recommend ISSHL treatment to take place within a carefully designed clinical trial with emphasis on comparativeness, internal and external validity.

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Chapter 4

DIAGNOSIS AND TREATMENT OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS:
a survey in the Netherlands and Flanders

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Introduction

Diagnosis and treatment of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) remain controversial entities in otology. When ISSHL is diagnosed "per exclusionem", discussion arises about its definition and the applied clinical analysis. Choice of treatment is perhaps even more contradictory.
We report the extent of (dis)agreement on diagnosis and treatment of ISSHL within the Dutch language region. We questioned all ENT-surgeons practising in the Netherlands and in Flanders (Dutch speaking part of Belgium) on definition, diagnosis, possible etiology, therapy and treatment results in ISSHL. We recommend a more rational approach to diagnosing and treating ISSHL.

Methods

A questionnaire containing 10 multiple-choice questions was designed. The questions concerned definition, incidence, diagnosis, treatment and follow-up of ISSHL. Respondents were also asked to judge several etiological hypotheses, and to estimate their treatment results. The questionnaire was validated by the Office for Medical Technology Assessment of the University Hospital Groningen. All 373 ENT-surgeons practising in the Netherlands and all 215 ENT-surgeons practising in Flanders received the questionnaire. Data were processed anonymously on an IBM compatible personal computer, using dBASE V (Borland International) and QuattroPro I (Borland International). Statistical analysis was performed using SPSS VI (SPSS inc.).

Response

In the Netherlands, 373 ENT-surgeons received our questionnaire. 240 forms were returned of which 10 forms were not filled in properly. 230 forms were included in this study (62%). In Flanders, 215 ENT-surgeons received our questionnaire. 51 forms were returned of which 1 form was not filled in properly. 50 forms were included in this study (23%). In total, we report the opinion of 280 ENT-surgeons (48%) practising in the Dutch language region, containing approximately 21.5 million inhabitants.

Results

Definition of ISSHL: Diagnostic criteria (Table 1)
"Hearing loss of unknown origin" was used as a diagnostic criterion by 83% of the Dutch ENT-surgeons and by 69% of the Flemish ENT-surgeons. The sensorineural nature of the hearing loss was considered a diagnostic criterion by 74% of the Dutch

and 76% of the Flemish respondents. The suddenness of hearing loss was important to 72% of the respondents in the Netherlands and to 54% of the respondents in Flanders. Hearing loss occurring within at most 24 hours was generally considered "sudden". For 57% of the Dutch respondents and 40% of the Flemish respondents, the severity of the hearing loss should average at least 30 dB. The extent of hearing loss, indicated by the number of frequency steps in the standard pure-tone audiogram involved in hearing loss, was a diagnostic criterion for 47% of the Dutch, and 42% of the Flemish respondents. Hearing loss occurring in 3 out of 7 steps in frequency (125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz) was required minimally to diagnose ISSHL.

Exclusion criteria were used by both the Dutch and the Flemish ENT-surgeons in diagnosing ISSHL. A recent trauma capitis (69% v. 60%) or a recent barotrauma (67% v. 58%) was frequently mentioned as exclusion criterion. A compromised otological history (42% v. 30%) or the recent use of potentially ototoxic medication (55% v. 34%) was used less often as an exclusion criterion for diagnosing ISSHL.

Definition of ISSHL, by application of diagnostic criteria, differed between the two groups of respondents. A statistically significant difference in opinion existed between the Dutch and Flemish ENT-surgeons regarding the unknown origin, the suddenness and the severity of the hearing loss, and to the recent use of potentially ototoxic medication. ($p \leq 0.05$, Chi-square test)

Table 1: Definition of ISSHL: diagnostic criteria.

Diagnostic criteria in ISSHL	**NL** n=230	**F** n=50
hearing loss of unknown origin*	83%	69%
sensorineural hearing loss	76%	74%
sudden hearing loss*	72%	54%
hearing loss averages at least 30 dB*	57%	40%
no. of audiogram frequencies in which hearing loss occurs	47%	42%
absence of recent trauma capitis	69%	60%
absence of recent barotrauma	67%	58%
compromised otological history	42%	30%
recent use of potentially ototoxic medication*	56%	34%

* difference statistically significant ($p \leq 0.05$, Chi-square test)

Incidence of ISSHL
In the Netherlands, 228 of 229 respondents (99.6%) diagnosed ISSHL. In Flanders, all 50 respondents diagnosed ISSHL. On average, the individual ENT-surgeon diagnosed ISSHL 3.0 (range 0.1 - 40) times annually in the Netherlands and 4.4 (range 1 - 20) times annually in Flanders.

Diagnosis of ISSHL (Table 2a-e)
a. Clinical examination
In cases of sudden hearing loss, otoscopy was performed by 99.6% of the Dutch and by all of the Flemish ENT-surgeons, inspection of the nasopharynx by 49% v. 62%, rhinoscopia anterior by 41% v. 52%, inspection of the oropharynx by 37% v. 50%, palpation of the neck by 37% v. 30% and indirect laryngoscopy by 27% v. 26%. A general physical examination was performed by 16% of the Dutch and 18% of the Flemish ENT-surgeons. The extent of clinical evaluation was comparable between both groups. ($p \leq 0.05$, Chi-square test)

Table 2a: Diagnosis of ISSHL: clinical examination.

Clinical examination in ISSHL	**NL** n=230	**F** n=50
otoscopy*	99,6%	100%
inspection of nasopharynx*	49%	62%
rhinoscopia anterior*	41%	52%
inspection of oropharynx*	37%	50%
palpation of the neck*	37%	30%
indirect laryngoscopy*	27%	26%
general physical examination*	16%	18%

* differences not statistically significant ($p > 0.05$, Chi-square test)

b. Audiovestibular evaluation
Pure-tone audiometry was performed by 96.6% of the Dutch and 98% of the Flemish respondents. Speech audiometry was performed by 84% of the Dutch and 34% of the Flemish respondents. Tuning fork tests according to Weber and Rinne were used frequently (82% v. 80%) by both groups. Impedance measurements were performed by 69% of the Dutch and 80% of the Flemish respondents. Stapedial reflex analysis was performed by 51% and 76%, Brainstem Evoked Response Audiometry (BERA) was performed by 64% and 82% of the Dutch and Flemish respondents respectively. Evaluation of nystagmus using glasses according to Frenzel was done by 34% of the Dutch and 54% of the Flemish ENT-surgeons. Electronystagmography evaluation

using caloric provocation was done by 46% of the Dutch and 68% of the Flemish respondents. Rotational chair provocated electronystagmography was performed by 17% of the Dutch respondents and by 54% of the Flemish respondents.
The extent of the audiovestibular evaluation in ISSHL differed between both countries. A statistically significant difference was found in the application of speech audiometry, stapedial reflex measurement, BERA, the use of glasses according to Frenzel and electronystagmography. ($p \leq 0.05$, Chi-square test)

Table 2b: Diagnosis of ISSHL: audiovestibular evaluation.

Audiometric evaluation in ISSHL	**NL** n=230	**F** n=50
pure-tone audiometry	96,6%	98%
speech audiometry*	84%	34%
tuning fork testing	82%	80%
impedance measurements	69%	80%
stapedial reflex evaluation*	51%	76%
Brainstem Evoked Response Audiometry (BERA)*	64%	82%
glasses according to Frenzel*	34%	54%
electronystagmography with caloric provocation*	46%	68%
electronystagmography with rotational chair provocation*	17%	54%

* difference statistically significant ($p \leq 0.05$, Chi-square test)

c. Laboratory investigations
Full blood cell count and differentiation (78% v. 82%), erythrocyte sedimentation rate (68% v. 44%), and serum electrolytes (52% v. 72%) were the laboratory investigations most often performed in ISSHL patients in the Netherlands and in Flanders. Paired virus serology (38% v. 64%) and VDRL (41% v. 54%) were also frequently determined in both the Netherlands and Flanders. Evaluation of the haemostatic pathway (15% v. 30%), immunoglobulin levels (16% v. 38%), Monosticon test (8% v. 6%) Paul Bunnell test (11% v. 26%), Wasserman (32% v. 18%), Anti Nuclear Cytoplasmatic Antigens (ANCA), Anti Nucleic Antigen (ANA), Anti double string DNA (15% v. 40%), Mycoplasma pneumoniae serology (3% v. 6%) and Borrelia burgdorferi serology (20% v. 26%) took place less often.
The extent of laboratory evaluation differed considerably between the Netherlands and Flanders. Only full blood cell count and differentiation, VDRL, Monosticon, Mycoplasma pneumoniae and Borrelia burgdorferi serology were performed equally

often. All other laboratory investigations differed significantly in frequency. (Chi-square test, $p \leq 0.05$)

Table 2c: Diagnosis of ISSHL: laboratory evaluation

Laboratory evaluation in ISSHL	**NL** n=230	**F** n=50
full blood count and differentiation	78%	82%
erythrocyte sedimentation rate*	67%	44%
serum electrolytes*	52%	72%
paired virus serology*	38%	64%
VDRL	41%	54%
Wasserman*	32%	18%
haemostatic pathway*	15%	30%
immunoglobulins*	16%	38%
Monosticon	8%	6%
Paul Bunnell*	11%	26%
ANCA, ANA, Anti ds-DNA*	15%	40%
Mycoplasma Pneumoniae serology	3%	6%
Borrelia Burgdorferi serology	20%	26%

* difference statistically significant ($p \leq 0.05$, Chi-square test)

d. Imaging techniques

Computed tomography of temporal bones and skull base was frequently performed in ISSHL in the Netherlands (54%) and in Flanders (62%). Magnetic resonance imaging of temporal bones and skull base was also used frequently in the Netherlands (44%) and in Flanders (52%). X-ray projections according to Schüller and Stenvers were seldom used in the Netherlands (13% respectively 11%) and in Flanders (4% respectively 2%). A standard thoracic X-ray was rarely made in ISSHL (4% v. 8%).
The use of scanning techniques was comparable in both countries. Conventional projection techniques were performed significantly less often in Flanders ($p \leq 0.05$, Chi-square test).

Table 2d: Diagnosis of ISSHL: imaging techniques.

Imaging in ISSHL	**NL** n=230	**F** n=50
CT-scan temporal bones and skull base	54%	62%
MRI temporal bones and skull base	44%	52%
X Schüller*	13%	4%
X Stenvers*	11%	2%
X Thorax	4%	8%

* difference statistically significant ($p \leq 0.05$, Chi-square test)

e. Consultation of other specialties

Neurologist (40%) and internist (34%) were frequently consulted in the Netherlands, and in Flanders (46% and 28%). Consultation of ophthalmologist (8% v. 12%) and immunologist (7% v. 8%) occurred less frequently. No statistically significant differences were found between both countries. ($p \leq 0.05$; Chi-square test)

Table 2e: Diagnosis of ISSHL: consultation of other specialities

Other specialities in ISSHL	**NL** n=230	**F** n=50
internist*	34%	28%
neurologist*	40%	46%
ophthalmologist*	8%	12%
immunologist*	7%	8%
cardiologist*	1%	6%

* differences not statistically significant ($p > 0.05$, Chi-square test)

Treatment (Table 3 a-b)

a. Delay

The interval between occurrence of ISSHL and initiation of treatment appears to be of prognostic significance[1]. This was important to 77% of the Dutch and 68% of the Flemish ENT-surgeons. In the Netherlands, 12 (range 1-31) days after the occurrence of hearing loss, treatment was generally considered to be fruitless; in Flanders, this was 20 (range 3-60) days after hearing loss occurred.

b. Therapy

In the Netherlands, ENT-surgeons frequently prescribed corticosteroids in ISSHL (63%). Rest was often advised (53%). In Flanders, corticosteroids were prescribed by 84% and rest was advised by 32% of the responding ENT-surgeons. Vasodilators (37% v. 78%), plasma-expanders (24% v. 26%) and anticoagulants (17% v. 22%) were used less frequently in ISSHL in both the Netherlands and in Flanders. Anti-histamines (16% v. 6%), Calcium-entry-blockers (9% v. 10%), CO_2 inhalation (5% v. 22%) and contrast dyes (1% v. 0%) were rarely applied in ISSHL in both countries. Eight percent of the Dutch respondents did not treat ISSHL at all.

Steroids, vasodilators and CO_2 inhalation are prescribed more often in Flanders. In the Netherlands, rest is advised more frequently and the decision not to treat ISSHL is more common. ($p \leq 0.05$, Chi-square test) Other treatment modalities are used to a comparable extent in the Netherlands and Flanders.

Table 3a: Treatment of ISSHL

Treatment of ISSHL	**NL** n=230	**F** n=50
corticosteroids*	63%	84%
(bed)rest*	53%	32%
vasodilators*	37%	78%
plasma-expanders	24%	26%
anticoagulants	17%	22%
anti-histamines	16%	6%
Calcium-entry blockers	9%	10%
CO_2 inhalation*	5%	22%
contrast dyes	1%	0%
no treatment*	8%	0%

* difference statistically significant ($p \leq 0.05$, Chi-square test)

c. Clinical and ambulant treatment

In the Netherlands, 52% of the ENT-surgeons considered hospital admission necessary for treatment of ISSHL. Seventy-six percent of their Flemish colleagues admitted ISSHL patients. Hospital stay averaged 7 days in the Netherlands and 5 days in Flanders. An outpatient follow-up was performed by 97% of Dutch and 98% of Flemish respondents. The duration of follow-up varied between 6 and 12 months in both countries.

d. Treatment results

Thirty-four percent of the Dutch ENT-surgeons and 18% of the Flemish ENT-surgeons estimated their therapy to result in usable hearing in 0 - 25% of their ISSHL cases. Thirty-five percent of the Dutch, versus 46% of the Flemish respondents estimated achieving usable hearing in 25 - 50% of their ISSHL cases. Seventeen percent of the Dutch, versus 28% of the Flemish respondents estimated to achieve this result in 50 - 75% of their ISSHL cases. One respondent claimed success in treating each ISSHL case. Both groups were comparable in estimating hearing recovery, although the Flemish ENT-surgeons were less pessimistic in estimating usable hearing in 0-25% of their cases. ($p \leq 0.05$, Chi-square test)

Table 3b: Estimated treatment results in ISSHL

Treatment results in ISSHL	**NL** n=230	**F** n=50
usable hearing in 0 - 25% of cases*	34%	18%
usable hearing in 25 - 50% of cases	35%	46%
usable hearing in 50 - 75% of cases	17%	28%
usable hearing in 75% -100% of cases	1%	0%

* difference statistically significant. ($p \leq 0.05$, Chi-square test)

Conceptions about the etiology of ISSHL (Table 4)

A disturbance of labyrinthine blood circulation (71% v. 66%) and viral labyrinthine infection (55% v. 70%) were most often postulated as a cause for ISSHL in the Netherlands and in Flanders. Thirty percent versus 32% of respondents suggested ISSHL to be the result of an underlying autoimmune disease. An acute hydrops of the labyrinth was thought to be the cause of ISSHL by 14% of the respondents in both countries. Thirteen percent versus 16% assumed labyrinthine membrane ruptures to cause ISSHL. A viral etiology is significantly preferred in Flanders ($p \leq 0.05$, Chi-square test). The other hypotheses are supported to the same extent in both countries.

Table 4: Conceptions about the etiology of ISSHL

Supposed etiology of ISSHL	**NL** n=230	**F** n=50
disturbance of labyrinthine blood circulation	71%	66%
viral labyrinthine infection*	55%	70%
underlying autoimmune disease	30%	32%
acute labyrinthine hydrops	14%	14%
labyrinthine membrane rupture	13%	16%

* difference statistically significant ($p \leq 0.05$, Chi-square analysis)

Discussion

On average, Idiopathic Sudden Sensorineural Hearing Loss is diagnosed 3.0 times annually by the Dutch ENT-surgeon. His Belgian colleague makes this diagnosis 4.4 times annually. In the Netherlands an incidence of 8 new cases of ISSHL per 100,000 inhabitants can be estimated. An incidence of 14.6 new cases per 100,000 inhabitants can be estimated in the Dutch speaking part of Belgium. These numbers are comparable to the incidence of ISSHL reported in the USA (10.7 new patients per 100,000 inhabitants per annum[1]) and to the incidence of ISSHL reported in Japan (13.7 new patients per 100,000 inhabitants[2]).

The sudden occurrence of sensorineural hearing loss of enigmatic etiology is a diagnostic criterion for the majority of respondents. On average, hearing loss must occur within 24 hours to be considered 'sudden'. The severity of the hearing loss is also frequently considered to be a diagnostic criterion, its severity being at least 30 dB, its extent averaging at least 3 of 7 one octave steps in frequency. Exclusion of events possibly related to hearing loss is regarded as important. Otological and medication history are less important for establishing the diagnosis of ISSHL. Flemish ENT surgeons use less stringent diagnostic criteria when diagnosing ISSHL. ISSHL is diagnosed more often in Flanders when compared to the Netherlands. Systematic application of in- and exclusion criteria in sudden hearing loss, therefore, seems to lead to a reduction in the number of cases considered to be idiopathic.

ISSHL is a diagnosis per exclusionem. Therefore, in our opinion, a careful evaluation is of paramount importance for each patient suspected of sudden hearing loss in order to prevent diagnostic omissions.
We found considerable shortcomings in the thoroughness of ISSHL evaluation. In a majority of ISSHL cases a complete ENT-examination is not performed and laboratory evaluation is incomplete. Audiological evaluation is performed thorough

in the Netherlands, but speech audiometry, estimating functional hearing, is performed by a minority of ENT-surgeons in Flanders. Vestibular evaluation is more thorough in Flanders, thus elucidating an early prognostic factor. Although modern imaging techniques are applied in ISSHL, this evaluation is lacking in a significant proportion of ISSHL patients, thereby underestimating retrocochlear and systemic causes of sudden hearing loss. Disagreement on diagnostic procedures in ISSHL between individual ENT-surgeons is reflected by the large differences found between Dutch and Flemish ENT-surgeons. The estimation of legal consequences and the method of health care financing differs between both countries and might vary between individual ENT-surgeons.

When treating ISSHL, a time interval is often used after which treatment of ISSHL is considered to be fruitless. Corticosteroids are frequently prescribed as the only treatment modality that has proven to be beneficial in ISSHL [3,4,5]. Treatment is often accompanied by advising the patient to rest. This advice probably has a more intuitive than scientific foundation. In a majority of cases, treatment modalities of ISSHL lack scientific foundation and can be considered to be potentially harmful [5,9]. While in the Netherlands monotherapy is often advocated in ISSHL, in Flanders a combination of various treatment modalities is used more often. A combination of treatment modalities in ISSHL does not possess significant advantages[9]. The treatment results as estimated by the responding ENT-surgeons are comparable to the spontaneous recovery rate of ISSHL, reported in the literature to occur in 45-65% of cases[1,10,11].
Viral labyrinthine infection and disturbance of cochlear blood flow are two hypotheses frequently mentioned in the literature as causes of ISSHL[11]. Our respondents also frequently mentioned these hypotheses as possible causes of ISSHL.

Recommendations

We find it desirable to define ISSHL more precisely, thereby limiting ISSHL to the truly idiopathic cases. This can be implemented by the use of a diagnostic protocol based on a differential diagnosis, thereby preventing diagnostic omissions.
Fundamental research aimed at elucidating the etiology of ISSHL might lead to further agreement on diagnostic and therapeutic procedures. Treatment results have been quite disappointing to this date. We therefore recommend treating ISSHL patients within a carefully designed clinical trial.

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Chapter 5

THE ETIOLOGY OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS: *experimental herpes simplex virus infection of the inner ear*

Stokroos RJ, Albers FWJ, Schirm J. The etiology of idiopathic sudden sensorineural hearing loss: experimental herpes simplex virus infection of the inner ear. Am J Otol. In press.

Introduction

The enigmatic pathophysiology of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) has elicited divergent hypotheses on its etiology.
A disturbance of labyrinthine blood circulation provoking ISSHL has been postulated because its abrupt onset resembles other infarctions of the central nervous system. However, the wide age distribution and the average cardiovascular risk as observed among ISSHL patients is not in accordance to this hypothesis[1-4]. Experimentally induced hearing loss of vascular origin is irreversible due to extensive cochlear fibrosis and ossification[5-7]. These were not found in ISSHL in both post mortem temporal bone histopathological examination[8] and in inner ear imaging studies [9] . Hearing recovers spontaneously in 45-65% of ISSHL-patients[10,11]. Therefore, it is not entirely satisfactory to assume a labyrinthine blood circulation disturbance to be responsible for a large proportion of ISSHL-cases.
A rupture of inner ear membranes might explain both the suddenness and the spontaneous recovery found in ISSHL, but clinical evidence is limited[12,13]. Although a severe hearing loss can be provoked experimentally by inducing a double labyrinthine membrane rupture[14], temporal bone histopathology of ISSHL patients does not provide evidence of (previous) membrane breaks[8]. Therefore, this hypothesis lacks convincing clinical and histopathological evidence too.
Several systemic viral infections are able to provoke sudden hearing loss. The observation of viral upper respiratory infection often preceding ISSHL led to the supposition of viral cochlear labyrinthitis to cause ISSHL[15]. Reports of seroconversion of herpes antibody titers in ISSHL[16,17] and the presence of latent neurotropic herpes viruses in the spiral ganglia of asymptomatic individuals[18], has drawn attention to the role of the herpes virus family in causing ISSHL. Further support for a viral etiology of ISSHL can be deduced from detailed descriptions of post mortem temporal bone histopathology of individuals with ISSHL who deceased of unrelated causes and from post mortem temporal bone histopathology of patients having suffered from viral labyrinthitis. The histopathological changes as observed in the temporal bones of ISSHL patients showed resemblance to the temporal bone pathology of patients with viral labyrinthitis[8, 19-22]. Histopathology in ISSHL as described in the literature is summarized in table 1.
Schuknecht et al.[8,19,20] described post mortem temporal bone histopathology of twelve cases of ISSHL. Light microscopic studies of the inner ear showed a variable degree of atrophy of the organ of Corti in 6 cases, a combination of pathological changes in the tectorial membrane and atrophy of the organ of Corti in 2 cases and pathological changes in the tectorial membrane only in 2 cases. In 7 of 12 cases, a variable degree of atrophy was seen in the stria vascularis. Loss of cochlear neural population was present in 3 cases. No cochlear pathology was found in the one case in which hearing returned to normal before decease. Yoon et al.[21] reported post mortem temporal bone histopathology in 5 cases of ISSHL. Atrophy of the organ of Corti, pathological changes of the tectorial membrane, atrophy of the stria vascularis and loss of cochlear neurons and nerve fibres were found. Sando et al.[22] reported light microscopic

findings in 2 patients having suffered from ISSHL and found atrophy of the organ of Corti in combination with atrophy of the tectorial membrane and the stria vascularis and a decrease in the number of cochlear nerves.

Table 1: Cochlear histopathology in Idiopathic Sudden Sensorineural Hearing Loss

	Schuknecht[8,19,20]	Yoon[21]	Sando[22]
Perilympathic			
Scala tympani	0	0	0
Scala vestibuli	?	?	?
Endolymphathic			
Stria vascularis	+	+	+
Reissner's membrane	0	0	0
Basilar membrane	0	0	0
Sensory end-organ			
Organ of Corti	+	+	+
Tectorial membrane	+	+	+
Neural structures			
Ganglion cells	+	+	+
Nerve fibres	+	+	+

(+: damaged, 0: normal, ?: unknown)

In a description of human post mortem temporal bone histopathology in Ramsay Hunt syndrome by Blackley et al.[23], perineural and intraneural lymphocytic infiltrations were observed in cochlear structures. The stria vascularis appeared atrophied, the organ of Corti was partially degenerated and covered by a collapsed Reissner's membrane. Zajtchuk et al.[24] described cochlear histopathology in Ramsay Hunt syndrome in which hearing had returned to normal before decease. On light microscopy, except for a slight detachment of the tectorial membrane, no cochlear abnormalities were found.

The key to successful treatment of any pathological condition lies in the understanding of its pathophysiology. In ISSHL, the delicacy of the structures involved obliges us to develop a model to study its pathophysiology. Based on the earlier summarized evidence, the herpes virus family might play an etiological role in provoking ISSHL by causing a subclinical viral labyrinthitis. The development of an animal model in which herpes induced viral labyrinthitis can be studied, might help us to solve some of the enigmas surrounding ISSHL.

Material and methods

Thirteen healthy male albino guinea pigs (weight 400-500 g.) with a positive Preyer reflex received Halothane® general anaesthesia. Via a retroauricular incision, the tympanic bulla of the left ear was exposed and opened. A bevelled glass pipette (World Precision Instruments), with a tip measuring 50 micrometres in diameter was introduced through the round window membrane into the perilymphatic space, using a micromanipulator (World Precision Instruments). Via a microdosage system (Mitutoya), two microlitres of a herpes simplex virus type 1 (HSV-1) suspension were injected in two minutes into the perilymphatic space. HSV-1, McIntyre strain, was grown in monolayers of human embryonic lung fibroblasts, using culture medium consisting of minimal essential medium and Hanks' salts supplemented with fetal calf serum. When the fibroblasts showed an extensive cytopathic effect, the culture supernatant was cleared by centrifugation at 2000 r.p.m. for 10 minutes. This cleared supernatant, which contained 8 x 10^4 $TCID_{50}$ units per microlitre, was used for infecting the guinea pigs.
Two groups were formed: 4 animals received the culture medium only and functioned as a control group, 9 animals were inoculated with the virus suspension. Each day, auditory function monitoring using the Preyer reflex[25] and vestibular function monitoring using the head tilt reflex was performed. Blood samples were obtained both prior to inoculation and just before sacrifice and HSV antibody titers were determined in both samples in the following two different ways. Complement fixing HSV antibodies were measured by a modification of the Laboratory Branch Complement Fixation micromethod[26], which can also be applied on sera from guinea pigs[27]. HSV-specific IgG titres were determined by indirect immunofluorescence on acetone fixed HSV-infected cells, using fluorescein isothiocyanate-labeled goat anti-guinea pig IgG reagent (Soutern Biotechnology Associates Inc.). On day seven, all animals were sacrificed. Primary fixation was performed by intralabyrinthine perfusion with 2.5% glutaraldehyde in a 0.08 mol/L sodium cacodylate buffer (pH =7.4). After dissection of the cochlea, immersion fixation with the same fixative was carried out during three hours. Decalcification took place in 10% EDTA-2Na (pH= 7.4). Postfixation was performed using 1% OsO_4 and 1.5% $K_4Ru(Cn)_6$ followed by dehydration in graded alcohol. After embedding, midmodiolar sections of the cochlea were stained toluidine blue and evaluated using light microscopy (Olympus OM2) and transmission electron microscopy (Philips EM201, 60 kV) by a panel of four independent observers experienced in the evaluation of inner ear pathology.

Results

Audiovestibular function

Animals inoculated with the culture medium only showed no sign of hearing loss or vestibular dysfunction. All the animals inoculated with HSV-1 showed an absent

Preyer reflex in the inoculated ear, indicating hearing loss. Hearing did not recover. No vestibular dysfunction was observed in these animals during the experimental period.

Serology

No systemic symptoms of herpes infection were observed in any of the animals. However, HSV-IgG seroconversions were demonstrated in all HSV inoculated animals and in none of the control animals. HSV-IgG titers in the second serum samples, of the infected animals, as measured by immunofluorescence, varied between 10 and ≥ 80 (median titer 20). No HSV antibodies were found when the less sensitive complement fixation test was used.

Light Microscopy (Table 2)

In the animals which were inoculated with the culture medium only, no structural or morphological changes were observed in the cochlea. In all animals inoculated with HSV-1, we found some blood cells in the scala vestibuli. In the scala tympani, these blood cells were embedded in a loose peripheral network of fibrosis, but a large central lumen remained. In the scala media, no blood cells or fibrosis were observed. Reissner's membrane had a normal appearance in most animals.

Table 2: Cochlear histopathology in experimental herpes simplex type 1 viral labyrinthitis

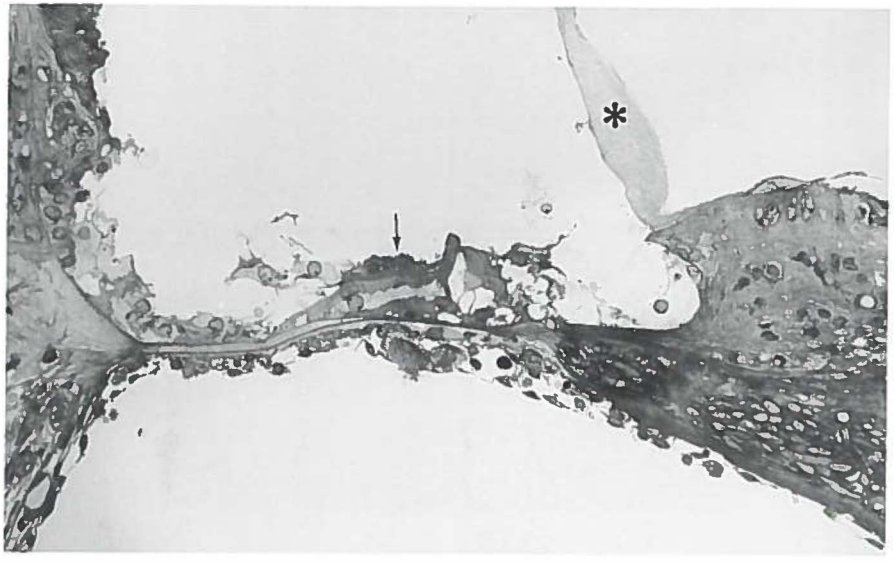
	HSV-1	**Culture medium**
Perilympatic		
Scala tympani	0/+	0
Scala vestibuli	++	
Endolymphatic		
Stria vascularis	++/+++	
Reissner's membrane	0	0
Basilar membrane	0	
Sensory end-organ		
Organ of Corti	++/+++	0
Tectorial membrane	+/++	
Neural structures		
Ganglion cells	+	0
Nerve fibres	++	

(+++ = destroyed, ++ = damaged, + = slight damage, 0 = normal)

The stria vascularis showed a disturbed architecture (fig. 1): in the intermediate cell layer, blood vessels showed an increased diameter and were filled with erythrocytes. The stria vascularis had a swollen appearance with the presence of increased intercellular spaces in the intermediate cell layer. Extensive histopathological changes were observed in the organ of Corti. The supporting cells (inner and outer pillar cells, inner and outer phalangeal cells) were very difficult to recognize due to morphological changes. The sensory cells were frequently replaced by the supporting cells. Outer and inner hair cells had disappeared completely in the basal windings, but in two animals, they could be recognized with difficulty in the apical coils. The tunnel of Corti was not recognizable. The tectorial membrane showed an increased distance from the organ of Corti, but its shape remained unchanged (fig. 2). Ganglion cells and neural structures showed a lymphocellular infiltration.

Figure 1: Light microscopy of the stria vascularis in experimental HSV-1 labyrinthitis (250x). Dilated vessels and erythrocyte sludging (arrow). Swollen appearance and increased intercellular spaces in the intermediate cell layer (asterisk).

Figure 2: Light microscopy of the organ of Corti in experimental HSV-1 labyrinthitis (250x). Extensive destruction of the organ of Corti and supporting cells. The tectorial membrane is disrupted from the sensory cells, but has a normal appearance (arrow).



Transmission Electron Microscopy

Reissner's membrane appeared thickened on light microscopic evaluation in some of our animals. Transmission electron microscopy (TEM) showed an intact basement membrane between the thin mesothelial cell layer and the epithelial cell layer. The epithelial cells possessed a multilobulated, ovoid nucleus and a well-developed Golgi complex. Its cell junctions were normal (fig. 3).
The tectorial membrane is observed to elevate or loosen from the organ of Corti and from the limbus spiralis in many cases of HSV-1 viral labyrinthitis. TEM evaluation showed a disturbed relation between interdental cells and the tectorial membrane (fig. 4).

Figure 3: Transmission electron microscopy of Reissner's membrane in experimental HSV-1 labyrinthitis (15000x), showing cell junctions between epithelial cells: zonula occludens (ZO), followed by zonula adhaerens (ZA) and desmosomes (D).

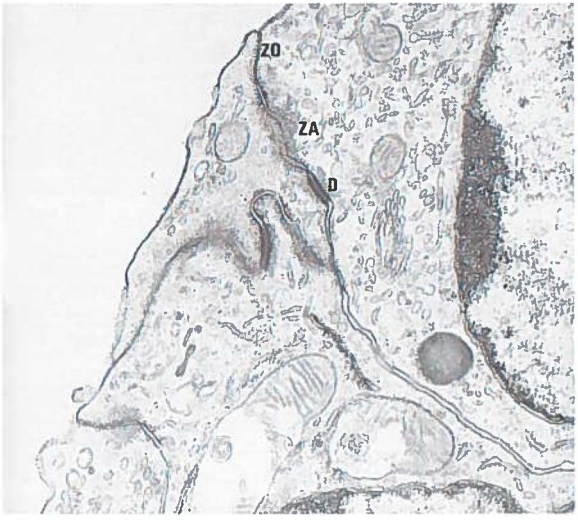
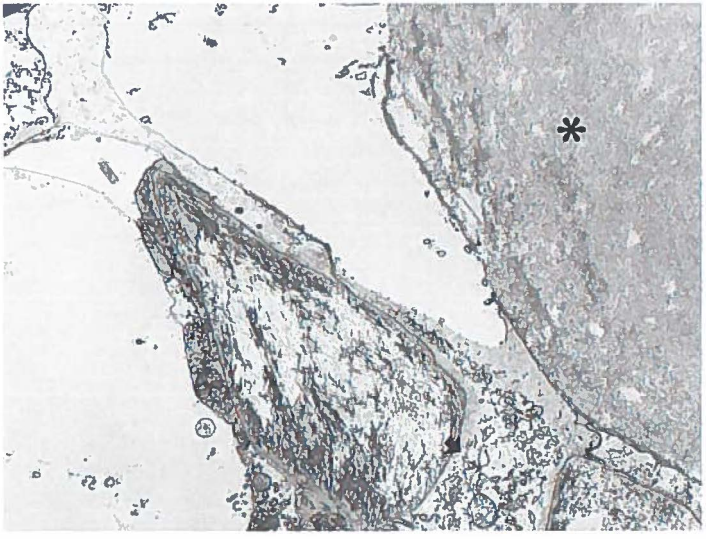


Figure 4: Transmission electron microscopy of the tectorial membrane in experimental HSV-1 labyrinthitis (4500x). Elevation of the tectorial membrane (asterisk) from the limbus spiralis might be due to damaged interdental cells (arrow) or secondary to elevation of the membrane.



Discussion

Experimentally induced HSV-1 labyrinthitis, causing both hearing loss and gross structural damage to the cochlea, followed an otherwise symptomless course which was not accompanied by the appearance of HSV specific complement fixing antibodies. However, primary HSV infection could be confirmed by HSV-IgG seroconversion. Whether a non-primary local HSV infection, as might be present in ISSHL, can also be detected by HSV-IgG serology remains to be demonstrated.
Experimental viral labyrinthitis has been induced by different inoculation routes, including inoculation along intralabyrinthine, middle ear, intracerebral, intraperitoneal and intranasal pathways and inoculation via the maternal placenta[28-37]. All extralabyrinthine inoculation routes differ in bypassing natural barriers and in the way the virus spreads to the cochlea. This introduces a variability into the experimental model we find unacceptable. It has been argued by several authors that irrespective of the inoculation route, viral affinity exists for various cochlear structures so the virus involved will leave a fingerprint on the affected cochlea. However, after intralabyrinthine/perilymphatic inoculation, a consistent perilymphatic inflammation is observed which can not be established in descriptions of the human cochlea in viral labyrinthitis. Although a selective viral affinity for other cochlear structures is apparent also after intralabyrinthine inoculation, we believe that the extent of perilymphatic involvement should be judged with caution when using this inoculation route. In spite of this limitation, we regard the intralabyrinthine inoculation model superior to other inoculation models.
From the literature on experimental viral labyrinthitis the following specific affinity for cochlear structures can be derived for various viruses[31-37] (Table 3):

1. Atrophy of the stria vascularis in HSV, mumps virus and vaccina virus.
2. Malformations of the tectorial membrane in HSV, mumps virus, rubeola virus and vaccina virus.
3. Atrophy of the organ of corti in HSV, mumps virus, rubeola virus, influenza virus and vaccina virus.
4. Loss of neuronal cochlear population in cytomegalovirus, HSV, mumps virus, rubeola virus and influenza virus.

Table 3: Experimental viral labyrinthitis: selective affinity of labyrinthine structures

	CMV	HSV	Mumps	Rubeola	Influenza	Vaccina
Perilymphatic						
Scala tympani	+[31,34,37]	+[31,33,36]	0[32,33]	+[32,33]	+[32,33]	+[32,33]
Scala vestibuli	+[31,34,37]	+[31,33,36]	?	?	?	?
Endolymphatic						
Stria vascularis	0[31,34,37]	+[31,33,36]	+[32,33]	0 [32,33]	0[32,33]	+[32,33]
Reissner's membrane	0[31,34,37]	0[31,33,36]	+[32,33]	0 [32,33]	0[32,33]	+[32,33]
Basilar membrane	0[31,34,37]	0[31,33,36]	+[32,33]	0 [32,33]	0[32,33]	+[32,33]
Sensory end-organ						
Organ of Corti	0[31,34,37]	+[31,33,36]	+[32,33]	+[32,33]	+[32,33]	+[32,33]
Tectorial membrane	0[31,34,37]	+[31,33,36]	+[32,33]	+[32,33]	+[32,33]	+[32,33]
Neural structures						
Ganglion cells	0[31]+[34,37]	+[31,33,36]	+[32,33]	+[32,33]	+[32,33]	0 [32,33]
Nerve fibres	+[31,34,37]	+[31,33,36]	+[32,33]	+[32,33]	+[32,33]	0 [32,33]

(+: affected, 0: normal, ?: unknown)

Only HSV and mumps virus are able to affect the same cochlear structures as are damaged in ISSHL. However, in mumps virus labyrinthitis, damage to the membranes surrounding the endolymphatic structures is observed, which is not described in HSV labyrinthitis and in ISSHL.

We found histopathological changes in the cochlea after inducing viral labyrinthitis by the HSV-1 to show a constant pattern of severe damage to the stria vascularis, atrophy of the organ of Corti, elevation or loosening of the tectorial membrane and inflammation of the neural fibres and ganglia. Reissner's membrane kept its normal architecture. Elevation of the tectorial membrane might be caused by a disruption of the interdental cells, but this could also be secondary to elevation of the membrane.

This pattern of pathological changes found in experimental HSV-1 labyrinthitis bears a strong resemblance to the histopathology of ISSHL, although in these cases the time interval between occurrence of ISSHL and observation of cochlear histopathology is obviously much longer than in our experimental design.

Conclusions

Experimental herpes simplex type 1 viral labyrinthitis provides a matching pattern of cochlear damage when compared to patients who have suffered from ISSHL. Severe deterioration of cochlear structure and function can occur without associated systemic manifestation of the viral infection, which is comparable to ISSHL too. These findings provide further support for the hypothesis that viral labyrinthitis might play an important role in the pathophysiology of ISSHL. The outcome of our study provides an adequate animal model for further elucidating the pathogenesis and treatment modalities in ISSHL.

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Chapter 6

THERAPY OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS: *antiviral treatment of experimental herpes simplex virus infection of the inner ear*

Stokroos RJ, Albers FWJ, Schirm J. Therapy of idiopathic sudden sensorineural hearing loss: antiviral treatment of expermental herpes simplex infections of the inner ear. Ann Otol Rhinol Laryngol. In press.

Introduction

Therapy of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) is a subject of controversy. The high spontaneous recovery rate of ISSHL (45-65 %)[1,2] and the low incidence of ISSHL (8-14.6 per 100,000) in the Netherlands and Flanders[3] make validation of empirical treatment modalities difficult, and its unknown pathophysiology impedes a rational approach. Earlier therapeutic efforts were aimed at restoring a supposed impaired cochlear blood circulation, but treatment results did not exceed placebo results[4]. Early application of corticosteroids has a modest beneficial effect on hearing recovery in ISSHL, but its interference with cochlear pathophysiology in ISSHL remains unclear[5,6].
In the literature, an important role of viral cochlear labyrinthitis in the pathogenesis of ISSHL is assumed, based on clinical and serological evidence and on a strong resemblance of cochlear histopathology found in experimental labyrinthitis and in post mortem temporal bone histopathology in ISSHL patients[7]. We have developed an animal model of ISSHL, in which herpes simplex virus type 1 (HSV-1) elicits sudden sensorineural hearing loss in the guinea pig inner ear (chapter 5). In treatment of other manifestations of herpetic infections, the combination of corticosteroids and aciclovir seems to possess a synergetic therapeutical effect[8]. In this study an animal experiment was performed to evaluate the influence of steroids and aciclovir (Zovirax®), either as a monotherapy or as a combination therapy on cochlear function and cochlear pathology in experimental HSV-1 labyrinthitis. The results may contribute to a more substantive approach to the treatment of ISSHL.

Material and methods

Sixteen healthy male albino guinea pigs (weight 400-500 g.) with a positive Preyer reflex received Halothane® general anaesthesia. Via a retroauricular incision, the tympanic bulla of the left ear was exposed and opened. An bevelled glass pipette (World Precision Instruments), with a tip measuring 50 micrometres in diameter was introduced through the round window membrane into the perilymphatic space, using a micromanipulator (World Precision Instruments). Via a microdosage system (Mitutoya), two microlitres of a herpes simplex virus type 1 (HSV-1) suspension were injected in two minutes into the perilymphatic space. HSV-1, McIntyre strain, was grown in monolayers of human embryonic lung fibroblasts, using culture medium consisting of minimal essential medium and Hanks' salts supplemented with fetal calf serum. When the fibroblasts showed an extensive cytopathic effect, the culture supernatant was cleared by centrifugation at 2000 r.p.m. for 10 minutes. This cleared supernatant, which contained 8 x 10^4 $TCID_{50}$ units per microlitre, was used for infecting the guinea pigs.
Four groups were formed: 3 animals were inoculated with the virus suspension and remained untreated, 3 animals were inoculated with the virus suspension and were treated with prednisolone, 3 animals were inoculated with the virus suspension and

were treated with aciclovir (Zovirax®, GlaxoWellcome), 3 animals were inoculated with the virus suspension and treated with both aciclovir and prednisolone. An additional group of four animals received the culture medium only. Prednisolone was administered in a dosage of 1 milligram per kilogram body weight intraperitoneally once daily during 7 days, aciclovir was applied in a dosage of 10 milligram per kilogram body weight intraperitoneally 3 times daily during 1 week. Each day, auditory function was monitored using the Preyer reflex. Blood samples were obtained both prior to inoculation and just before sacrifice, and HSV antibody titers were determined in both samples in both samples in the following two different ways. Complement fixing HSV antibodies were measured by a modification of the Laboratory Branch Complement Fixation micromethod[9], which can also be applied on sera from guinea pigs[10]. HSV-specific IgG titres were determined by indirect immunofluorescence on acetone fixed HSV-infected cells, using fluorescein isothiocyanate-labeled goat anti-guinea pig IgG reagent (Soutern Biotechnology Associates Inc.). On day seven, all animals were sacrificed. Primary fixation took place by intralabyrinthine perfusion with 2.5% glutaraldehyde in a 0.08 mol/L. sodium cacodylate buffer (pH =7.4). After dissection of the cochlea, immersion fixation with the same fixative was carried out during three hours. Decalcification took place in 10% EDTA-2Na (pH= 7.4). Postfixation was performed using 1% OsO_4 and 1.5% $K_4Ru(Cn)_6$ followed by dehydration in graded alcohol. After embedding, midmodiolar sections of the cochlea were stained with toluidine blue and evaluated using light microscopy (Olympus OM2) and judged by a panel of four independent observers experienced in the evaluation of inner ear pathology.

Results

Observation of auditory function

The Preyer reflex, estimating the presence of hearing, was positive before inoculation with HSV-1 in all animals. Hearing loss occurred in the affected ear within 24 hours in all animals inoculated with HSV-1. The animals inoculated with the culture medium showed no sign of hearing loss.
In the untreated group, hearing did not recover. In the prednisolone treated group, hearing recovered by 7 days. In the aciclovir treated group, hearing did not recover. In the aciclovir / prednisolone treated group, hearing recovery occurred after 2-3 days.

Serological evaluation

No systemic symptoms of viral infection were observed in any of the animals. However, HSV-IgG seroconversions were demonstrated in all HSV inoculated animals and in none of the control animals. HSV-IgG titers in the second serum samples, of the infected animals, as measured by immunofluorescence, varied between 10 and ≥ 80 (median titer 20). No HSV antibodies were found when the less

sensitive complement fixation test was used.

Light microscopic evaluation (Table 1)

In animals inoculated with the culture medium and in all contralateral ears of the HSV inoculated animals, the perilymphatic spaces showed no sign of bleeding or fibrosis. Reissner's membrane was intact. The stria vascularis showed its normal architecture. The supporting cells were normal and the outer and inner hair cells were intact. The tectorial membrane was in its normal position, the tunnel of Corti had its normal shape. Cochlear neural fibres and spiral ganglion cells were not affected.

Table 1: Structural changes of the cochlea in experimental herpes simplex virus type 1 (HSV-1) labyrinthitis and its treatment.

	HSV-1	**HSV-1/ prednisolone**	**HSV-1/ aciclovir**	**HSV-1/ prednisolone + aciclovir**
Scala vestibuli	+	0/+	+	0/+
Scala tympani	+/++	+/++	++	+
Scala media	0	0	0	0
Reissner's membrane	0	0	0	0
Stria vascularis	++/+++	++	++/+++	0/+
Supportive cells	++/+++	++	+++	++
Outer hair cells	+++	++/+++	+++	+/++
Inner hair cells	+++	+++	+++	++
Tectorial membrane	++	++	++	+
Nerve fibres	++	+	++	0/+
Ganglion cells	++	+	++	0/+

(+++: destroyed, ++: damaged, +: slight damage, 0: normal)

In animals inoculated with the HSV-1 (fig.1), we found some blood cells lying peripherally in the scala vestibuli. In the scala tympani, these cells were surrounded by a loose peripheral network of fibrosis. In the scala media, no blood cells or fibrosis were observed. Reissner's membrane was intact and in its normal position. The stria vascularis showed a disturbed architecture: the intermediate cell layer showed dilated blood vessels which were filled with erythrocytes. The stria vascularis was swollen

with the presence of increased intercellular spaces in the intermediate cell layer. An inflammatory infiltration was present in the stria vascularis and in the spiral ligament. Supportive cells were flattened or destroyed. Outer and inner hair cells were completely shrivelled up. The tunnel of Corti was not recognizable. The tectorial membrane was elevated from the organ of Corti and in some cases lying loose in the scala media but its shape remained unchanged. Both nerve fibres and ganglion cells showed some inflammatory infiltration.

In the animals treated with prednisolone after inoculation (fig. 2), some blood cells were present in the apical portion of the scala vestibuli. This bleeding was more profound in the aciclovir treated group (fig. 3) and much less in the aciclovir-prednisolone treated group (fig. 4).

In the prednisolone treated group, the scala tympani showed a loose peripheral network of fibrosis lying peripherally in the basal coils of the cochlea. This fibrosis was more dense and accompanied by bleeding in the aciclovir treated group. In the aciclovir-prednisolone treated group, a very mild fibrosis lying peripherally in the basal coils was found. Reissner's membrane remained intact in all three groups.

The stria vascularis showed dilated blood vessels and inflammatory cells in the animals treated with prednisolone and, more pronounced, in the animals treated with aciclovir. When both prednisolone and aciclovir were applicated, pathological changes were almost totally absent.

The supportive cells were flattened and damaged in the animals receiving prednisolone. This was more pronounced in the animals receiving aciclovir as a monotherapy but considerably less in the apical coils of the animals receiving both treatment modalities.

Outer hair cell damage was severe in the prednisolone treated group, profound in the aciclovir treated group and less severe in the prednisolone-aciclovir treated group, in which the apical windings of the cochlea were unaffected. Inner hair cells were completely destroyed in both groups receiving monotherapy, and were damaged in the basal coils in the group receiving combination-treatment. The tectorial membrane was elevated in both groups receiving monotherapy but remained attached to the cochlea in the animals receiving the combination therapy.

A mild inflammatory reaction existed in nerve fibres and spiral ganglion cells of the animals receiving prednisolone-monotherapy, this reaction being greater in the animals treated with aciclovir only. In the group receiving the combination therapy, this reaction could not be established.

Figure 1: Light microscopy of a midmodiolar section of a guinea pig cochlea showing experimental herpes simplex virus type 1 labyrinthitis (100x).
Extensive destruction of the organ of Corti and supporting cells (arrow). The stria vascularis shows severe morphological degeneration (asterisk).

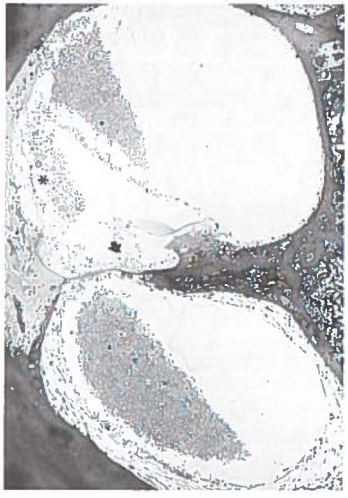

Figure 2: Light microscopy of a midmodiolar section of a guinea pig cochlea showing experimental herpes simplex virus type 1 labyrinthitis after treatment with prednisolone (100x).
Diminished destruction of the organ of Corti and supporting cells (arrow). Less bleeding in the scala vestibuli (asterisk).

Figure 3: Light microscopy of a midmodiolar section of a guinea pig cochlea showing experimental herpes simplex virus type 1 labyrinthitis after treatment with aciclovir (100x).
Severe destruction of the organ of Corti and supporting cells (arrows). Considerable bleeding in the scala vestibuli and scala tympani (asterisk).

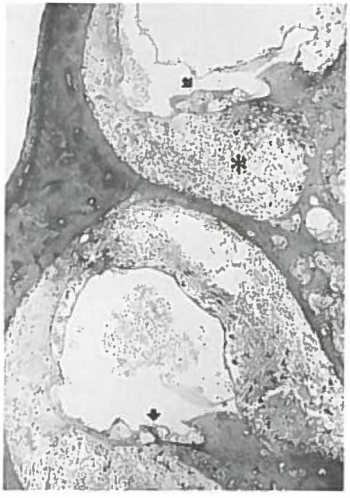

Figure 4: Light microscopy of a midmodiolar section of a guinea pig cochlea showing experimental herpes simplex virus type 1 labyrinthitis after treatment with prednisolone and aciclovir (100x).
The organ of Corti and supporting cells are much less affected (arrow). The stria vascularis has an almost normal architecture (asterisk).

Discussion

Auditory function

Preyer reflex monitoring was chosen because it provides a reproducable estimate of the presence of hearing without disturbance of the animal model, and in can be performed rapidly and repeatedly. In this study design, these advantages outweight the more precise estimate of hearing threshold obtained by measuring electrophysiological parameters[11]. Herpes simplex virus type 1 labyrinthitis caused rapid hearing loss which recovered within 7 days of treatment with prednisolone. This is consistent with our clinical experience. Although the application of aciclovir alone did not lead to hearing recovery, the combined treatment of HSV-1 labyrinthitis with both aciclovir and prednisolone led to earlier hearing recovery than observed with prednisolone as a monotherapy.

Serological evaluation

The experimentally induced HSV-1 labyrinthitis, causing both hearing loss and gross structural damage to the cochlea, followed an otherwise symptomless course which was not accompanied by the appearance of HSV specific complement fixing antibodies. However, the primary HSV infection in the inoculated animals could be confirmed by HSV-IgG seroconversion. Whether a non-primary local HSV infection, as might be present in ISSHL, can be detected by serological evaluation remains to be demonstrated.

Light microscopic evaluation

Histopathological changes in the cochlea after inducing viral labyrinthitis by HSV-1 showed a consistent pattern of severe damage to the stria vascularis, atrophy of the organ of Corti, elevation or loosening of the tectorial membrane and inflammation of the neural fibres and ganglia. These pathological changes show a strong resemblance to those described in ISSHL, although in these subjects, the time interval between occurrence of ISSHL and observation of cochlear histopathology is obviously much longer than in our experimental design. This might be responsible for the differences between our experimental observations and descriptions of ISSHL post mortem histopathology in the literature[7].
Early application of corticosteroids can suppress the inflammatory reaction to HSV-1, thereby limiting structural damage to the cochlea. However, significant destruction remains, perhaps explaining the modest success of ISSHL treatment with prednisolone. Application of antiviral medication as a monotherapy, aimed at the prevention of viral multiplication did not alter the devastating effects of HSV-1 labyrinthitis. Perhaps viral spreading is already too extensive when using the perilymphatic inoculation pathway. Theoretically, the combination of prednisolone and aciclovir will not only lead to a suppressive effect of the inflammatory reaction

but also to a limitation of viral multiplication and spreading. In this study, the combination of both prednisolone and aciclovir seems synergistic in limiting cochlear damage compared with prednisolone application as a monotherapy: less damage occurred to the organ of Corti and the stria vascularis, especially in the apical windings of the cochlea. Also, the inflammatory reaction found in neural structures seems to be limited further by this combined treatment.

Conclusions

Histopathogical changes caused by experimental HSV-1 labyrinthitis show a striking resemblance to histopathological changes described in ISSHL patients. Severe deterioration of cochlear function and of cochlear structures occurs, whilst no systemic manifestations of viral infection are observed. This provides further support for the hypothesis that ISSHL might be caused by a viral labyrinthitis, possibly involving the herpes virus family. Corticosteroids are able to alleviate hearing loss and to limit cochlear damage in experimental HSV-1 labyrinthitis. Adding aciclovir to prednisolone treatment provides earlier relief of the hearing loss and further limitation of structural cochlear damage in experimental HSV-1 labyrinthitis.
This combination therapy has already proven its effectiveness in Ramsay Hunt syndrome and in herpes zoster oticus. It has also been proposed for treatment of Bell's palsy[12]. The usefulness of early corticosteroid application in ISSHL has been reported in the literature. Our study results suggest a synergistic therapeutical effect of the combination of corticosteroids and aciclovir in the treatment of ISSHL. We are currently investigating this treatment modality in ISSHL patients in a randomized, double blind, placebo controlled clinical study.

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Chapter 7

MAGNETIC RESONANCE IMAGING OF THE INNER EAR IN IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

Stokroos RJ, Albers FWJ, Krikke AP, Casselman JW. Magnetic Resonance Imaging of the Inner Ear in Idiopathic Sudden Sensorineural Hearing Loss. Submitted.

Introduction

Sudden sensorineural hearing loss is a symptom which can be ascribed to a variety of etiological factors. Often, no etiology can be identified and the hearing loss is considered to be idiopathic. Hypotheses explaining the idiopathic manifestation of sudden sensorineural hearing loss include a labyrinthine circulatory disturbance, a spontaneous labyrinthine membrane rupture or a subclinical viral labyrinthitis. Although the exact mechanism operational in the pathogenesis of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) remains obscure, circumstantial evidence is pointing at a subclinical viral labyrinthitis[1].

Magnetic resonance imaging (MRI) is usually performed in sudden sensorineural hearing loss because its superior soft tissue contrast is able to distinguish underlying pathology, such as cerebellopontine angle lesions[2]. Advancements in MRI, especially the use of gadolinium contrast (Gd-MRI), refinement of its resolution and the application of special sequences, such as three-dimensional Fourier transformation-constructive interference in steady state (3DFT-CISS) MRI or fast spin-echo (FSE) MRI might provide further insight in labyrinthine pathology in ISSHL.

In labyrinthitis, disruption of the blood-labyrinth barrier causes protein accumulation in the intralabyrinthine fluid compartment, which might be detected as a high signal intensity on unenhanced T1-weighted MR images. Application of gadolinium contrast causes further intralabyrinthine enhancement by contrast leakage and accumulation. Some authors suppose that the distribution of labyrinthine enhancement is related to tonotopic projection of the hearing loss on the cochlea[3].

Mark, Seltzer et al.[3,4] reported seven patients with sudden hearing loss presumed to be idiopathic, in which a resolving hyperintensity of the inner ear was seen using T1-weighted images before and after gadolinium contrast application. Four other patients were suffering from a proven viral labyrinthitis, and showed a similar picture. Busaba and Rausch[5] reported Gd-MRI results of 14 ISSHL cases with an abnormal auditory brainstem response (ABR). In 1 case, enhancement was found in the distal portion of the internal auditory canal, which resolved in 6 weeks with concomitant hearing recovery. In all the other cases, Gd-MRI was normal.

Albers, Demuynk and Casselman[6] reported an MRI study of the inner ear in 5 ISSHL cases in whom hearing loss had existed for 5 months, using 3DFT-CISS MRI. The study was aimed at investigating late sequelae of ISSHL in the membraneous labyrinth. No enhancement or osseous obliteration of the perilymphatic spaces was found, which is often described in hearing loss associated with blood circulation disturbances and in bacterial labyrinthitis. Study results provided support for a viral labyrinthitis in the pathogenesis of ISSHL.

In Bell's palsy, Gd-MRI enhancement has been described along the course of the seventh cranial nerve[7,8], and in Ramsay-Hunt syndrome Gd-MRI enhancement of the inner ear and seventh and eight cranial nerves was found[9,10,11]. These findings were interpreted to denote inflammation of labyrinthine and neural structures.

Although the first two reports indicate the ability of Gd-MRI in detecting labyrinthine and neural inflammatory changes in the early phase of ISSHL, its sensitivity is

unknown.
We report early findings in the human labyrinth in ISSHL as detected by Gd-MRI, in relation to the severity of the hearing loss, eventual vestibular involvement and time interval between occurrence of ISSHL and MR imaging.

Subjects and methods

Thirty-six ISSHL patients took part in a prospective multicentre clinical trial aimed at investigating therapy with prednisolone / aciclovir versus prednisolone / placebo. We defined ISSHL as follows: (1) Sensorineural hearing impairment of unknown etiology. (2) Hearing impairment occurring within 24 hours. (3) Hearing impairment averages at least 30 dB for three subsequent one octave steps in frequency in the standard pure-tone audiogram. Exclusion criteria were: (1) A history of fluctuating hearing impairment. (2) A compromised otological history.
In all patients magnetic resonance imaging was performed. In one patient a schwannoma originating from the vestibular nerve was detected within the inner auditory canal. For adequate MR imaging of labyrinthine pathology, the following requirements were applied:

1. Imaging is obtained by using a superconductive active shielded magnet of at least 1.0 Tesla.
2. Sequences consist of both gadolinium-enhanced T1- and unenhanced T1-weighted images.
3. Slice thickness is 3 millimetres at maximum, excluding an eventual interslice gap.

MR images of 27 patients fulfilled these criteria and were included. Patients were investigated using a Philips Gyroscan S15 MR, a Siemens Magnetom Impact MR , a Siemens Magnetom Vision MR and a Signa MR.
The scans were judged independently by the authors. Visualisation of the membranous labyrinth on MRI was interpreted along the guidelines listed in table 1[12].
The following variables were correlated to the MRI findings:

1. Severity of hearing loss, as indicated by the Fletcher index.
2. Vestibular involvement, defined as an abnormal electronystagmographic response on caloric or rotational chair provocation.
3. Time interval between occurrence of ISSHL and imaging.

Table 1: Value of different MRI sequences in patients with membranous labyrinth pathology[12].

	T1	T2	T1Gd	T1+T2	T1+T1Gd	T2+T1Gd
Labyrinthitis	-	-	+	-	++*	+
Schwannoma	++	-	+	++	++*	+
Cholesterol granuloma	+	+	+	++*	+	+
Fibrous dysplasia	++	++	++	++	++	++
LVAS	++	++	++	++	++	++
Cogan's syndrome	-	-	-	-	-	-

(-) diagnosis not possible with this single sequence or pair of sequences.

(+) pathology was recognized, additional information provided by other sequences required to make exact diagnosis.

(++) diagnosis can be made with this single sequence or pair of sequences alone.

(*) optimal single sequence or pair of sequences in this case.

LVAS large vestibular aqueduct syndrome.

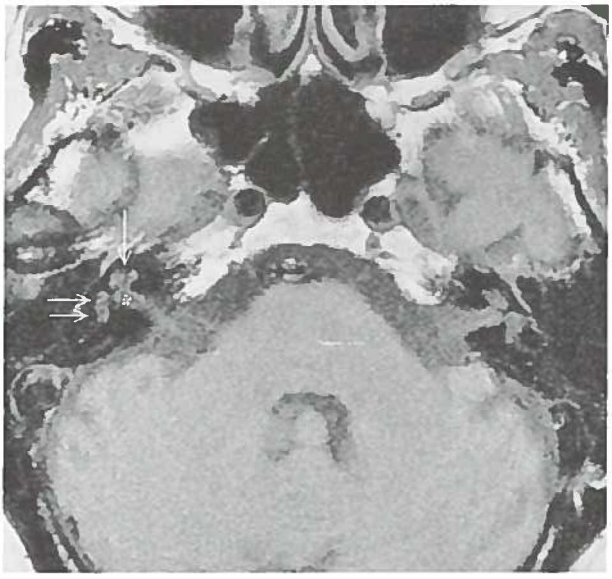
Results

In ISSHL, T1-weighted unenhanced and gadolinium enhanced MRI showed no abnormal enhancement in either the labyrinth or the cochleovestibular nerve in 26 of 27 patients (fig. 1). In one patient we observed mild enhancement in the basal and middle cochlear turns on T1-weighted images before and after gadolinium application. Constructive interference in steady state (CISS) sequences obtained in this study confirmed an earlier report[6], showing no osseous or fibrous obliteration of the perilymphatic spaces in ISSHL.

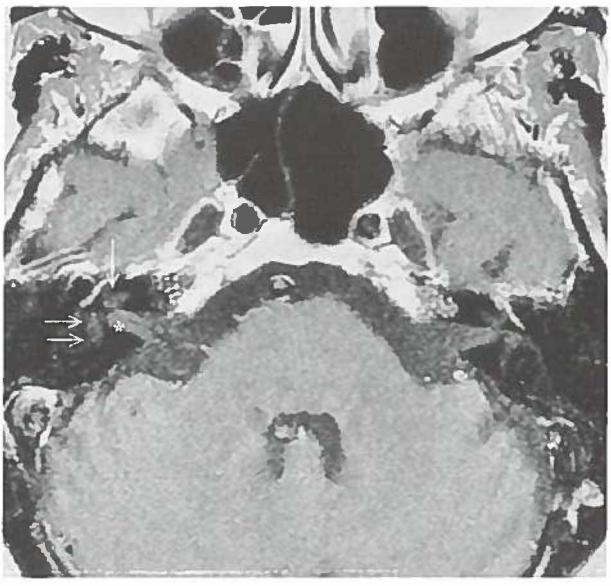
In 15 cases, the right ear and in 12 cases the left ear was involved. No cases of bilateral hearing loss were present. Hearing loss averaged 73.6 dB Fletcher index (range 40-120). Vestibular involvement was present in 6 cases. MRI was performed within one week after hearing loss occurred in 4 cases, within two weeks in 13 cases, within one month in 19 cases and within six weeks in 25 cases. In the patient showing abnormal labyrinthine enhancement, profound deafness (120 dB Fletcher index) with vestibular involvement had occurred 44 days before imaging.

Figure 1: Unenhanced (fig. 1a) and gadolinium enhanced (fig. 1b) MRI of the inner ear in ISSHL showing normal visualisation of the cochlea (arrow), vestibulum (double arrow) and cochleovestibular nerve (asterisk).

1a.



1b.



Discussion

ISSHL is characterized by its unknown etiology. Accumulating circumstantial evidence implies a subclinical viral labyrinthitis in eliciting ISSHL. Acute labyrinthitis can be recognized on gadolinium enhanced T1-weighted MR images as a result of gadolinium accumulation in the membraneous labyrinth caused by breakdown of the blood-perilymph barrier[12]. However, in our series of ISSHL patients labyrinthine enhancement on MRI is a rare finding. MRI enhancement of labyrinthine structures in ISSHL depends on the intensity of the underlying inflammatory process. In our study, in only 4 cases MR imaging was performed within one week after initial presentation of symptoms. The prolonged time interval between the onset of ISSHL and the moment of imaging might explain in part the absence of labyrinthine enhancement in our patients. All patients reported in this study were treated with the anti-inflammatory drug prednisolone and double-blindly with the antiviral drug aciclovir or with placebo, aimed at dampening the underlying labyrinthitis and thereby at improving hearing recovery prognosis[13,14]. Since the early treatment of ISSHL is of prognostic value, therapy was started as soon as possible after occurrence of hearing loss, and imaging was obtained afterwards. However, the anti-inflammatory therapy might have attenuated the viral labyrinthitis in our patients, making it undetectable by MRI.

The severity of the hearing loss and vestibular involvement provides an indication of the intensity of the labyrinthitis. ISSHL cases reported in this study represent the normal spectrum of clinical presentation of the disease when severity of the hearing loss and vestibular involvement are concerned[15]. Labyrinthine enhancement in our study exclusively occurred in a patient with severe audiovestibular symptoms indicating a profound labyrinthitis. In cases of mild hearing loss without vestibular involvement, MRI detection threshold might be too high.

Earlier reports confirm the ability of MRI to identify an underlying inflammatory process in ISSHL but provide no estimate of its sensitivity. The definition of ISSHL in this study is in accordance with the definitions applied in earlier imaging studies[3-5]. However, in these studies, additional selection criteria such as an abnormal auditory brainstem response (ABR) may have provided a selection bias, providing unjustified optimism in the ability of MRI to detect a labyrinthitis in ISSHL.

Traditionally, MRI is used to exclude cerebellopontine angle lesions in sudden hearing loss. It has again proven this ability in our study. However, MRI may play an important role in either identifying or excluding an extensive part of the differential diagnosis of sudden hearing loss. Intralabyrinthine localized lesions (e.g. schwannoma, autoimmune labyrinthitis in Cogan's syndrome), congenital malformations (e.g. large vestibular aqueduct syndrome) or central lesions (e.g. multiple sclerosis) can be detected by MRI[12]. Although MR imaging seems obligatory in each case of ISSHL, this is not common practice yet[16].

MRI should be performed as early as possible after ISSHL has occurred, thereby avoiding possible labyrinthine enhancement attenuation by interference with therapy or by spontaneous recovery.

When MRI is performed along the recommendations summarized in table 2, the requirements mentioned previously can be certified. Adequate judgement of labyrinthine enhancement is possible only when slice thickness of the T1-weighted images is (less than) 3 mm. An interslice gap should not be used when investigating an organ as small as the inner ear. At least T1-weighted images before and after gadolinium contrast application should be obtained of the labyrinth and cerebellopontine angle, but we recommend a complete imaging sequence of the auditory pathway in each ISSHL case. To reduce misinterpretation by partial volume effects, both axial and coronal slices should be made. Further insight in the distribution of labyrinthine pathology might be obtained by using three-dimensional reconstruction techniques. We have used gadolinium contrast in a dosage of 1 mg/kg body weight in this study, and we have no experience in increasing the gadolinium dosage. Theoretically, a higher gadolinium dosage might be able to ease detection of labyrinthine enhancement in ISSHL.

Table 2: Recommendations for Magnetic Resonance Imaging in Idiopathic Sudden Sensorineural Hearing Loss

ISSHL related	MRI related
- investigate each case of ISSHL	- use slice thickness ≤ 3 mm
- investigate as soon as possible after hearing loss	- use no interslice gap
- investigate preferably before treatment is started	- obtain at least T1 and T1Gd images
- study the complete auditory pathway	- obtain axial and coronal slices

Conclusions

Magnetic Resonance Imaging in ISSHL is valuable to exclude cerebellopontine angle lesions presenting as sudden hearing loss. In daily clinical practice, its sensitivity to identify an intralabyrinthine or neural inflammatory process in ISSHL is low. Such a process might only be observed in the very early phase after ISSHL occurred and might be attenuated by anti-inflammatory therapy. Therefore, we recommend an imaging protocol in which at least unenhanced T1- and gadolinium enhanced T1-weighted MR images are acquired as early as possible in ISSHL, preferably before treatment is started. This makes ISSHL not only an neuro-otological but also a neuro-radiological emergency.

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Chapter 8

ANTIVIRAL TREATMENT OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS:

a prospective, randomized, double blind clinical trial

Stokroos RJ, Albers FWJ, TenVergert EM. Antiviral treatment of idiopathic sudden sensorineural hearing loss: a prospective, randomized, double blind clinical trial. Acta Otolayngol (Stockh). In press.

Introduction

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) annually occurs in 8-14.6/100.000 persons in the Netherlands and Flanders but its pathophysiology and therapy remain subject to contradiction[1,2].

Etiology

A subclinical viral labyrinthitis was postulated to elicit ISSHL from observations of an upper respiratory infection preceding the hearing loss[3]. This hypothesis was supported by reports of seroconversion of viral antibody titers for several viruses in ISSHL[4-6]. MRI studies of the inner ear indicate the presence of a viral labyrinthitis[7,8]. Postmortem cochlear histopathology of ISSHL patients has shown pathological changes resembling those encountered in viral labyrinthitis[9-11]. Herpetic viral labyrinthitis provides a matching histopathological pattern of cochlear damage when compared to patients having suffered from ISSHL, and reactivation of a latent herpes infection was postulated to cause ISSHL[12]. Herpes simplex virus type 1 (HSV-1) has been demonstrated to remain latent in healthy human spiral ganglia[13]. We have elicited sudden hearing loss in the guinea pig by inducing HSV-1 labyrinthitis and found cochlear histopathology to resemble cochlear histopathology in ISSHL (Chapter 5). Experimental viral labyrinthitis by other virus families possesses a less comparable affinity to various cochlear structures[14-18]. Based on these findings, we have adopted the hypothesis that ISSHL might be caused by a reactivation of a subclinical labyrinthine infection, possibly by HSV-1.

Therapy

Therapy of ISSHL is disputable also. Its low incidence impedes empirical control of all treatment modalities possible. The early application of corticosteroids in ISSHL improves hearing recovery prognosis to a limited extent[19,20]. Other treatment modalities either are lacking proper evaluation or are ineffective[21]. In experimentally induced HSV-1 labyrinthitis in the guinea pig we found hearing to recover after application of prednisolone. Cochlear damage seemed to be limited by the anti-inflammatory properties of corticosteroids. Based on the hypothesis of viral reactivation we also used a combination therapy consisting of aciclovir (Zovirax®) and prednisolone. After this combination therapy we observed further limitation of cochlear damage and earlier hearing recovery (Chapter 6). This therapy modality is also favoured in other herpetic infections[22,23] but has not been reported in ISSHL. In this study, ISSHL therapy consisting of corticosteroids and aciclovir is applied in a prospective, randomized, double-blind clinical trial to make evaluation of this treatment modality possible.

Patients and methods

In- and exclusion criteria

Patients participating in the trial met the following inclusion criteria: (1) cochlear hearing loss of unknown etiology; (2) hearing loss averages at least 30 dB HL for three subsequent one octave steps in frequency in the standard pure tone audiogram; (3) hearing loss occurring within 24 hours; (4) blank otological history. Exclusion criteria were: (1) hearing loss occurring more than 14 days ago; (2) contraindications for the use of either prednisolone or aciclovir.

Diagnostic protocol

The interval between the occurrence of ISSHL and the onset of treatment is of prognostic significance[21]. The necessity for early treatment of ISSHL may implicate the erroneous treatment of various underlying conditions leading to a sudden loss of inner ear function that can only be identified by time consuming diagnostic procedures. Although most conditions are rare, their consequences might be important. Therefore, we use an extensive diagnostic protocol in each case of sudden hearing loss.. After diagnostic samples have been taken, a provisional diagnosis of ISSHL is made and treatment is initiated. When a cause for sudden hearing loss could be identified later, patients were excluded from the study.

Informed consent

Patients received oral explanation by the treating physician and written information by the investigator. They signed an informed consent, designed according to European Good Clinical Practice regulations before participating in the study.

Design

This study was designed as a prospective, multicenter, randomized, double-blind, placebo controlled clinical trial. A multicenter approach was chosen because the low incidence of ISSHL makes inclusion of a sufficient number of patients difficult. In each participating hospital, the medical ethical committee approved of the trial protocol.

ISSHL patients were admitted during one week for treatment. Randomization was performed by the hospital pharmacist. Treatment and follow-up were performed double-blindly. Patients were divided in two groups. Both groups were treated intravenously with prednisolone in a dosage of 1 mg per kg body weight on day one, to be diminished in equal steps during seven days to 0 mg. One group received aciclovir intravenously in a dosage of 10 mg per kg body weight, three times daily for seven days, the other group received placebo. Aciclovir or placebo was given in identical bottles labelled "ISSHL-trial". Outpatient follow-up consisted of four consultations, 1 week, 3, 6 and 12 months after discharge. After completion of the study, participating patients, treating physicians and investigators were informed whether aciclovir or placebo had been received.

Subjective parameters

Patients were asked to judge their hearing recovery, tinnitus intensity, pressure sensation and dizziness. Hearing could be categorized as worsened, equal or improved. Tinnitus, pressure sensation and dizziness could be categorized as absent, mild, moderate or severe. These parameters were recorded before and after hospitalization, and during outpatient follow-up.

Laboratory evaluation

Laboratory investigations were aimed at excluding the presence of an infectious, inflammatory or autoimmune process or a coagulopathy. An extensive virus serological evaluation was performed using paired blood samples and a nasopharyngeal swab or aspirate. Herpes simplex viruses, varicella zoster virus, cytomegalovirus, Ebstein-Bar virus, mumps virus, measles virus and chlamydiae were evaluated using specific IgG and IgM detection. Rubella virus was evaluated using IgM detection and hemagglutinase reaction (HAR). Mycoplasma pneumoniae was evaluated using IgM and complement fixing reaction. Influenza and parainfluenza viruses, rs-virus and coxiella burnetii were evaluated using complement fixing reaction.

Audiometric parameters

The following quantitative parameters were used to evaluate inner ear function on presentation:

(1) Pure-tone audiometry; (2) Speech audiometry; (3) Brainstem evoked response audiometry; (4) Nystagmography by caloric and torsion swing provocation.

Pure-tone and speech audiometry were repeated at discharge, and on an outpatient basis after one week and after three, six and twelve months.

Data collection and statistical processing

A case record form was used for data collection. Data processing took place using an IBM compatible personal computer. Statistical processing was performed using SPSS release 7.0 (SPSS Inc.). Data entry was controlled by frequency tables. An assumed normal distribution of the parameters were verified by Kolmogorow-Smirnow tests.

Performing a clinical trial in a relatively small patient cohort implies a sensitivity to unequal distribution of variables of prognostic significance, despite careful randomisation. In ISSHL, severity of the hearing loss and involvement of the vestibular apparatus are indicators of an unfavourable prognosis. The proportion of patients with vestibular involvement did not differ significantly between both groups. The severity of initial hearing loss did significantly differ between both groups but approximated a normal distribution in each group. Between groups hearing recovery results were analyzed using MANOVA covariate analysis, controlling for unequal initial hearing loss severity. The other variables were normally distributed and statistically processed using t-tests for independent samples and Chi-square analysis. A 5% significance level was used.

Results

General characteristics

Between 1994 and 1996, 44 Dutch and Flemish ISSHL patients were included in the study. Twenty-two patients received aciclovir and prednisolone and 22 patients received placebo and prednisolone. One patient was diagnosed as having a vestibular schwannoma and was excluded after randomisation. Subsequently, 43 patients were available for evaluation: 22 in the aciclovir/prednisolone and 21 in the placebo/prednisolone group. All cases of hearing loss were unilateral. Gender distribution was equal within both groups. In the whole group, age distribution ranged from 11-71 years, averaging 45.5 years with a preponderance for the fourth and fifth decades. In the aciclovir treated group age averaged 42.9 years, in the placebo group age averaged 45.7 years ($p > 0.05$). Within one month before hearing loss occurred, complaints of an upper respiratory infection had been present in 6/22 patients receiving aciclovir and in 7/21 patients receiving placebo ($p > 0.05$). In the whole population, a recent upper respiratory infection occurred in 13/43 patients (30%). A history of herpes labialis infection was found in 11/43 patients (26%) and a history of herpes zoster infection was found in 3/43 cases (7%). The occurrence of previous infections was equally distributed between aciclovir and placebo treated patients. On average, the hearing loss had been present for 4 days before specialist consultation took place (range 0-12 days). Patients delay did not differ between aciclovir and placebo treated patients. Median hearing loss occurred within 5 minutes in the whole group. In 9 cases, the hearing loss was present at awakening. No seasonal influence was established on occurrence of hearing loss in our patients.

Adverse effects

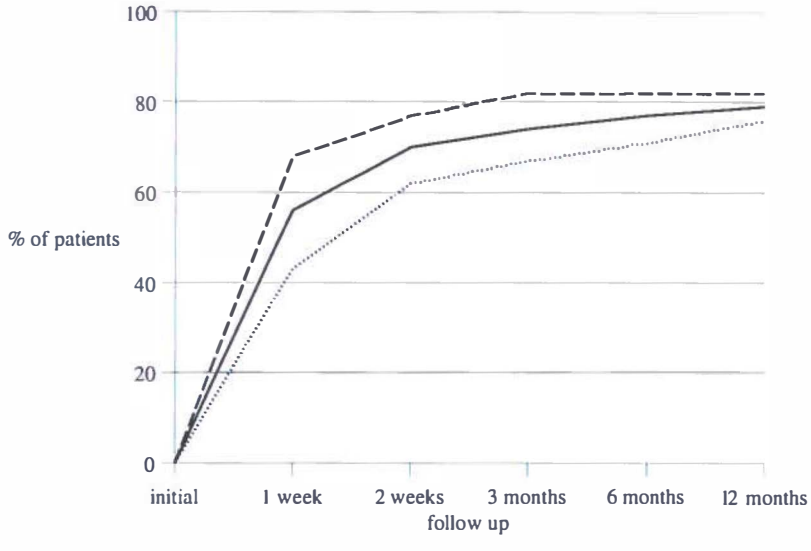
The following events were noticed during treatment: 4 patients complained of a headache, of which 3 received placebo and 1 received aciclovir. Slight to moderate nausea occurred once in the placebo and once in the aciclovir group. In the placebo group, 1 patient complained of stomach pain and 1 patient developed a reversible high blood glucose level. These two side effects were both interpreted to be the result from prednisolone administration. No specific aciclovir side effects were observed.

Virus serology

An intensive effort was made to demonstrate the presence of systemic viral infection. Although in none of our patients clinical symptoms of viral infection were found, in 5/43 patients serological signs of viral infection were present. A raised IgM antibody titer against varicella zoster virus was found in one patient. Seroconversion against rubella virus occurred once, and signs of an active, non primary Ebstein-Bar virus infection was demonstrated once also. A dubious IgM reaction against mumps virus existed in one patient, and in another patient, parainfluenza virus type 3 was cultured from the nasopharynx, without a concomitant rise in antibody titer.

Subjective parameters (fig.1a-d)
After one week of treatment, 15/22 (68%) of patients receiving aciclovir and 9/21 (43%) patients receiving placebo noticed hearing improvement ($p > 0.05$) (fig.1a).

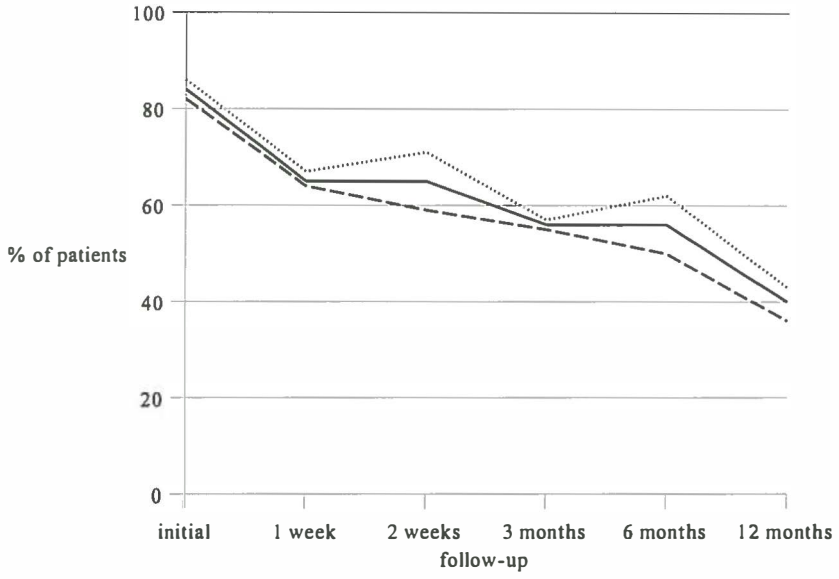
Figure 1a: Hearing categorized as "improved" by 43 ISSHL patients ($p > 0.05$).



In the remaining patients, hearing was judged to have remained unchanged. Hearing was not categorized as worsened after treatment in both groups. Most patients experienced hearing recovery during the first two weeks after hearing loss occurred. During follow-up, subjective hearing recovery took place in another 10/43 (23%) of patients. No significant differences were observed in hearing recovery between both groups.
Tinnitus appeared to be the most discomforting symptom to accompany ISSHL (fig.1b). 36/43 patients (84%) experienced tinnitus, either preceding, coinciding with or following hearing loss. Tinnitus persisted for 6 months in 24/43 (56%) of patients. Twelve months after hearing loss, 17/43 (40%) of patients still experienced tinnitus. Severity of tinnitus did not differ significantly among the categories mild, moderate and severe. No differences in tinnitus complaints were found between aciclovir and

placebo groups. Application of aciclovir did not change tinnitus prognosis.

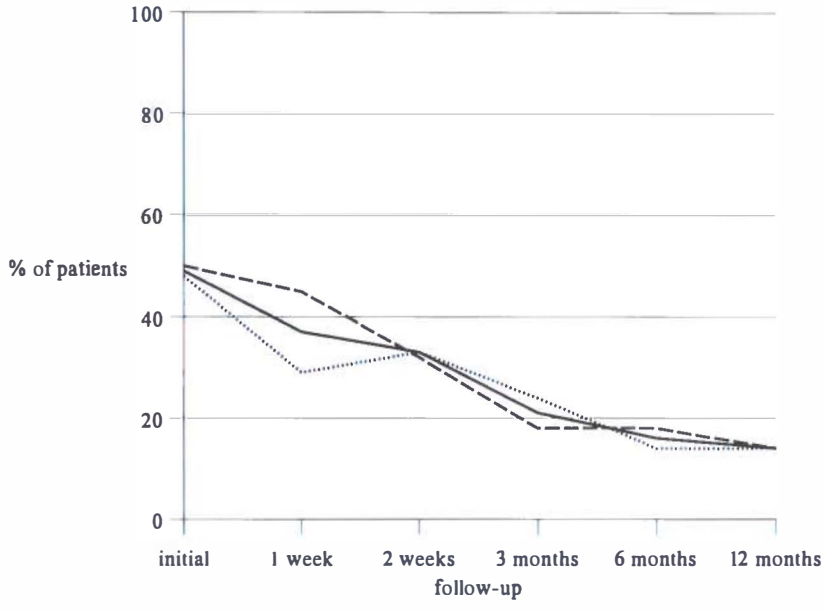
Figure 1b: Tinnitus categorized by 43 ISSHL patients ($p > 0.05$).



--- aciclovir/ prednisolone treatment (n = 22)
.... placebo/ prednisolone treatment (n = 21)
— both groups (n = 43)

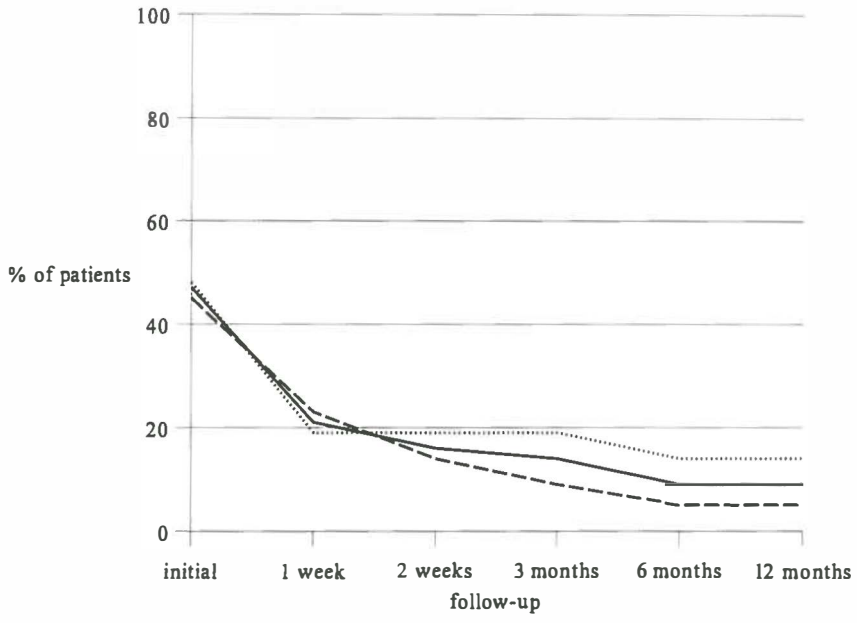
A pressure sensation on the affected ear was present in 21/43 patients (49%)(fig.1c). In 6 cases, this sensation preceded the hearing loss, in 7 cases it accompanied the hearing loss and in 8 cases it was noticed afterwards. In 6 cases pressure was judged to be mild, in 12 cases it was moderate and in 3 it was severe. In general, the prognosis of the pressure sensation was favourable: one year after the hearing loss, it was judged to be mild in 3 cases, moderate in 1 and severe in 2. Aciclovir or placebo treatment did not possess a statistically significant influence on this symptom.
Hearing loss was accompanied by a sense of disequilibrium or vertigo in 20/43 cases (47%) (fig.1d). In 11 cases this sensation became apparent after hearing loss occurred, in 7 it accompanied hearing loss and in 2 it preceded hearing loss. Vestibular complaints resolved quickly. The prognosis of vertigo was good: 12 months after hearing loss, 4 patients noticed a mild sense of disequilibrium.

Figure 1c: Pressure sensation categorized by 43 ISSHL patients ($p > 0.05$).



--- aciclovir/ prednisolone treatment (n = 22)
.... placebo/ prednisolone treatment (n = 21)
— both groups (n = 43)

Figure 1d: Vertigo / postural instability categorized by 43 ISSHL patients ($p > 0.05$).



--- aciclovir/prednisolone treatment (n = 22)
.... placebo/ prednisolone treatment (n = 21)
_ both groups (n = 43)

Audiometric parameters (Fig. 2a-e, fig 3a,b)
Hearing thresholds versus follow-up interval, as measured by pure-tone audiometry in dB Fletcher index (FI) for each patient receiving either aciclovir or placebo are depicted in figures 2a and 2b.
Hearing loss (dB FI) one week, two weeks and 12 months after ISSHL versus initial hearing loss are plotted for each individual case in figures 2c, 2d and 2e.
Pure-tone audiometry was used to categorize hearing recovery (fig. 3a). A hearing recovery larger than 10 dB FI within a follow-up interval was categorized as hearing improvement, a recovery of 10 dB FI or less was categorized as an unchanged hearing.
After treatment, in 18/43 (42%) patients a hearing recovery of more than 10 dB FI occurred. Two weeks after hearing loss, this was achieved by 28/43 (65%) of patients. One year after hearing loss, 34/43 (79%) of patients had obtained more than 10 dB FI hearing recovery. Differences in hearing improvement between aciclovir and placebo treated patients were not significant ($p > 0.05$).
Pure-tone audiometry was used also to quantify hearing recovery (fig. 3b).

Figure 2a: Hearing recovery in dBHL (FI) in 22 ISSHL patients receiving aciclovir/prednisolone.

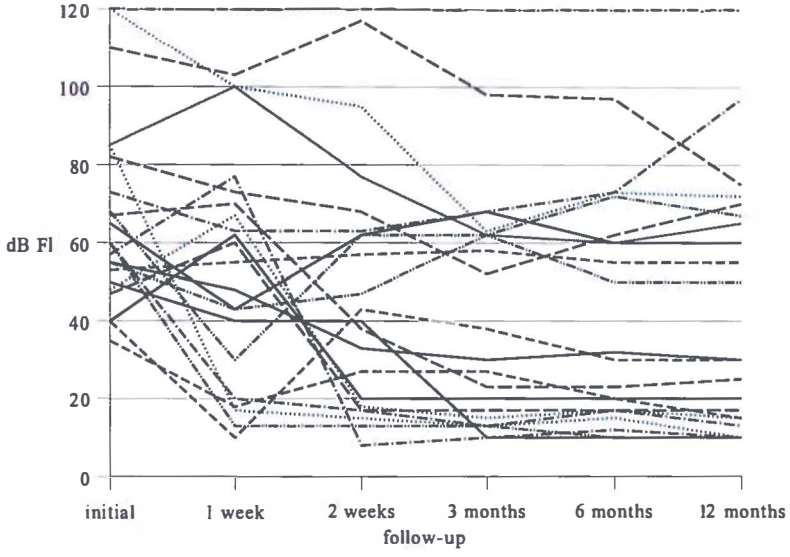


Figure 2b: Hearing recovery in dB HL (FI) in 21 ISSHL patients receiving placebo/prednisolone.

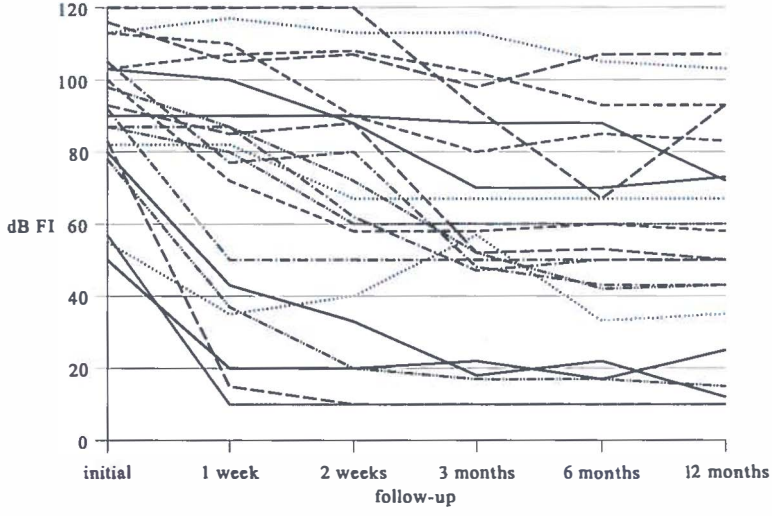


Figure 2c: Hearing recovery after one week versus initial hearing loss (dBHL FI) in 43 ISSHL patients, treated with either aciclovir/ prednisolone (▲) or placebo/prednisolone (o).

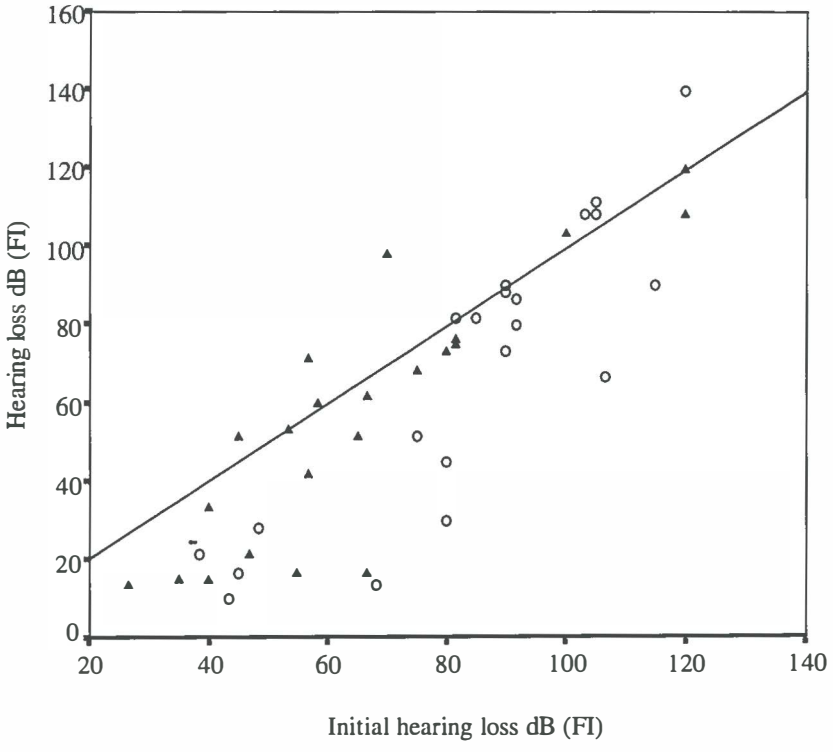
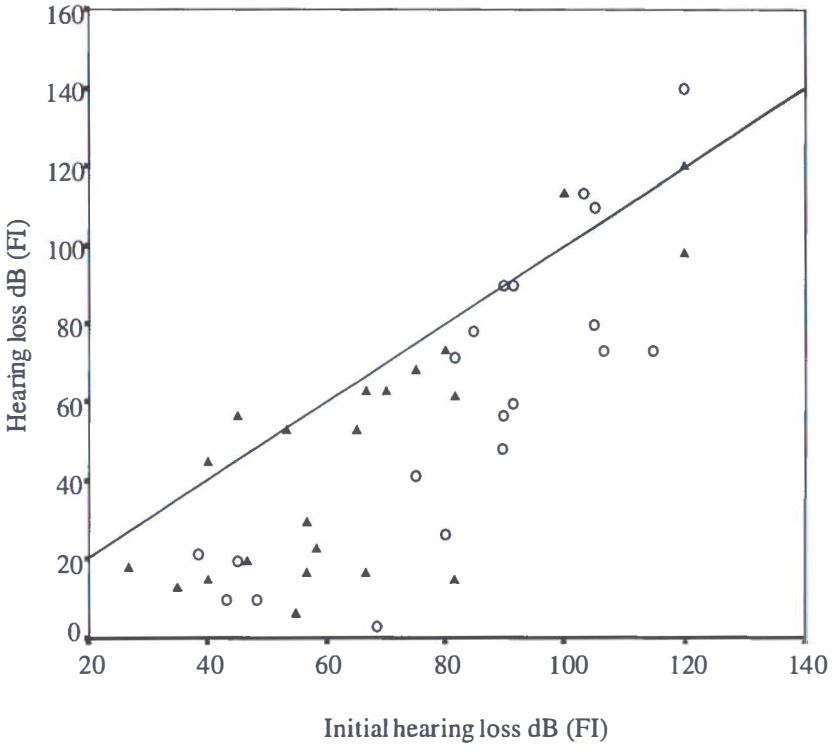
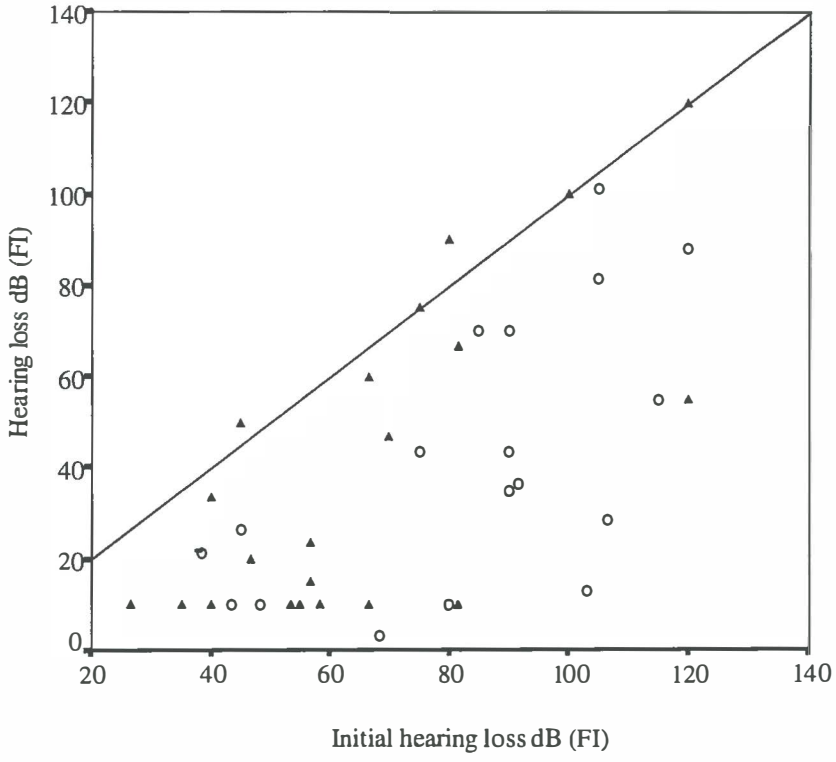


Figure 2d: Hearing recovery after two weeks versus initial hearing loss (dBHL FI) in 43 ISSHL patients, treated with either aciclovir/ prednisolone (▲) or placebo/prednisolone (o).



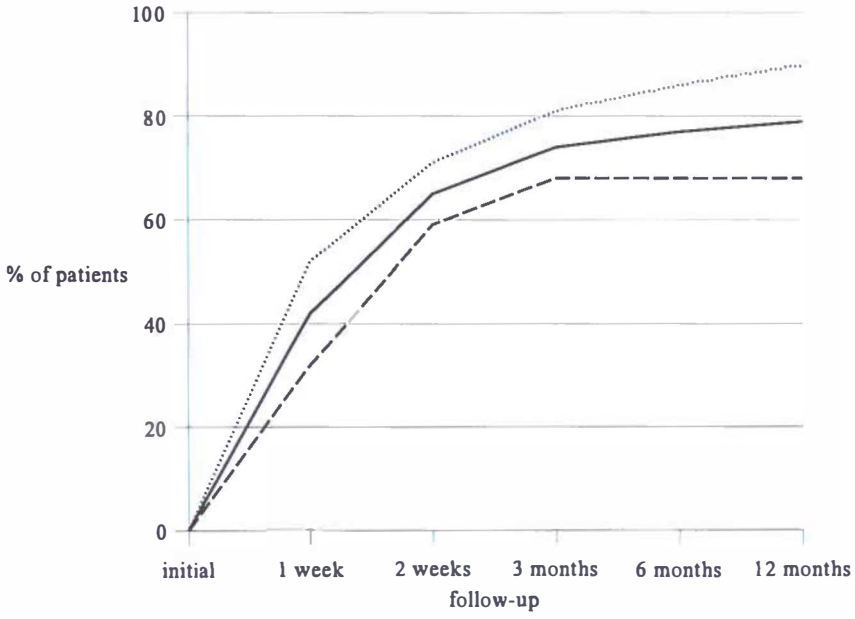
— no hearing recovery.

Figure 2e: Hearing recovery after twelve months versus initial hearing loss (dBHL FI) in 43 ISSHL patients, treated with either aciclovir/ prednisolone (▲) or placebo/prednisolone (o).



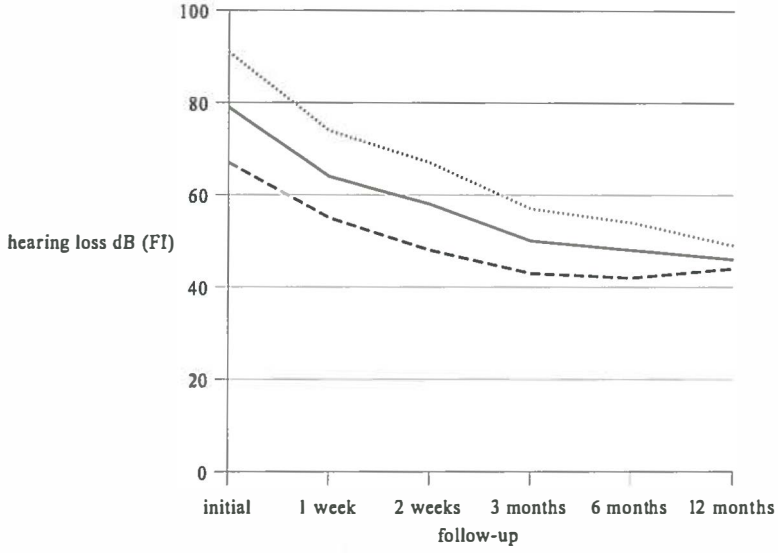
__ no hearing recovery

Figure 3a: Hearing improvement > 10 dB HL (FI) in 43 ISSHL patients ($p > 0.05$).



--- aciclovir/ prednisolone treatment (n = 22)
.... placebo/ prednisolone treatment (n = 21)
— both groups (n = 43)

Figure 3b: Hearing recovery by pure tone audiometry in 43 ISSHL patients ($p > 0.05$).



--- aciclovir/ prednisolone treatment (n = 22)
.... placebo/ prednisolone treatment (n = 21)
— both groups (n = 43)

On admittance, hearing loss averaged 79 dB FI (n=43). When treatment was completed, hearing had improved to 64 dB FI, further improving to 58 dB FI two weeks after hearing loss had occurred and to 50 dB FI 3 months after hearing loss. Six months after hearing loss, hearing thresholds averaged 48 dB FI and 12 months after hearing loss, 46 dB FI. In the aciclovir/prednisolone treated group, on presentation, hearing loss averaged 67 dB FI. Hearing loss after one week of treatment averaged 55 dB FI, after 2 weeks 48 dB FI, after 3 months 43 dB FI, after 6 months 42 dB FI and after 12 months 44 dB FI. In the placebo/prednisolone treated group, on presentation hearing loss averaged 91 dB FI. Hearing loss after one week of treatment averaged 74 dB FI, after 2 weeks 67 dB FI, after 3 months 57 dB FI, after 6 months 54 dB FI and after 12 months 49 dB FI.
In our clinical experience, prognosis is unfavourable in case of profound hearing loss. In 14/43 patients, initial pure-tone audiometry revealed a hearing loss > 100 dB (FI).

Patients with an initial hearing loss ≤100 dB FI had a better hearing recovery prognosis compared to patients with a hearing loss >100 dB FI irrespective of aciclovir application ($p < 0.001$).
Despite of our double-blind randomization, more cases of profound hearing loss were allocated to the placebo-treated group than to the aciclovir treated group, thereby giving the erroneous impression of a significantly better hearing prognosis in the patients treated with aciclovir. When this difference in severity of initial hearing loss was corrected for by performing covariate analysis, hearing recovery between the aciclovir/prednisolone and placebo/prednisolone treated patients did not differ significantly.
ISSHL is often regarded as an otological emergency. It is assumed that when treatment is initiated in the very early phase of the hearing loss, hearing recovery prognosis might be better. To verify this assumption, additional analysis was performed. We divided our patients into two subgroups: one in which treatment had begun within 24 hours after occurrence of hearing loss (n=12), and one in which treatment delay had been longer, at maximum 12 days (n=31). Hearing recovery prognosis turned out to be comparable in both subgroups ($p > 0.05$).
On average, a maximum speech discrimination score of 39% was achieved by patients when presenting with hearing loss. After one week of treatment, speech discrimination had improved to 56%, to reach 68% after 3 months. Speech discrimination ability did not improve further afterwards. The application of aciclovir had no effect on speech discrimination ability in ISSHL (MANOVA covariate analysis controlling for unequal speech discrimination distribution between both groups).
Involvement of the vestibular organ in the hearing loss, defined as an abnormal ENG response to caloric and/or rotational chair provocation of the affected ear, was present in 10/43 (23%) patients. Hearing loss and hearing recovery prognosis in this subgroup were comparable to hearing and hearing recovery in the population without vestibular involvement ($p > 0.05$).

Discussion and conclusions

ISSHL affects patients in the core of their existence and has serious repercussions on their social and professional functioning.
A majority of ISSHL patients treated with prednisolone experience some subjective hearing recovery. Most do so after one week of treatment. In our study, aciclovir treated patients did not experience hearing recovery earlier or more often. When evaluated by audiometry, hearing recovery prognosis did not benefit from the application of aciclovir. Subjective hearing improvement closely matched hearing improvement evaluated by pure-tone audiometry (fig.1a and 3a). A majority of patients suffer tinnitus, which has a poor prognosis, and turns out to be one of the lasting disturbing consequences of ISSHL. Application of aciclovir did not change tinnitus prognosis. Frequent concomitant complaints are a pressure sensation on the

affected ear and a sense of disequilibrium or vertigo. Both symptoms have a favourable prognosis, irrespective of aciclovir use.

Our ISSHL patients, treated with prednisolone, achieved a better hearing recovery compared to untreated ISSHL patients reported previously[21]. Although they are non-randomized groups, both share important characteristics. With this limitation in mind, our findings provide some additive support for earlier reports recommending the use of corticosteroids in ISSHL.

Prognostic factors in ISSHL mentioned in the literature are vestibular involvement, severity of initial hearing loss and audiogram shape. Prognosis of hearing loss with or without involvement of the vestibular organ was comparable in our patients, although vestibular involvement has been suggested to indicate a more elaborate labyrinthitis carrying a relatively unfavourable prognosis[2]. In our patients, in case of severe or profound hearing loss, the chances for hearing to recover are poor, in cases of mild or moderate hearing loss, the chances of hearing recovery are better. In severe or profound hearing loss, cochlear damage is probably already too extensive for therapy to have a beneficial effect. Pure-tone audiogram shape was difficult to categorize in our patients. We were not able to establish a relationship between hearing recovery prognosis and pure-tone audiogram shape.

In ISSHL, the delicacy of the structures involved makes elucidation of- and interference with its pathophysiology difficult. In our experience, no truly successful treatment regimen can be offered to the ISSHL patient, despite a mild beneficial effect of corticosteroids. Although we have not been able to ascertain a therapeutic value from the application of aciclovir in ISSHL in this study, some methodological limitations are apparent which might explain our results in part.

Despite a multicenter approach covering the whole Dutch language region (21.5 million inhabitants) the patient group under investigation might have been too small to achieve statistical significance. Almost every study concerning ISSHL therapy suffers from this limitation, because of its low incidence, especially when in- and exclusion criteria are applied strictly[21]. Secondly, to prove efficacy of a therapeutic modality in ISSHL it has to perform significantly better than the high spontaneous recovery rate found in ISSHL, reported between 40-65%. Thirdly, we experienced difficulty in defining desired outcome after therapy. Our efforts to perform a power analysis failed because the outcome measurements available are only a rough estimate of the sense of hearing. Most patients experience some hearing recovery but a minority recovers completely. Even if a few decibels are gained, speech discrimination ability is often impaired and the affected ear is no longer useful.

Fourthly, despite double-blind randomization we failed to control for severity of initial hearing loss in this study. In future ISSHL research, we consider using forward stratification for initial hearing loss severity.

We question whether the failure to demonstrate the effectiveness of aciclovir therapy in ISSHL should have implications for speculations on the pathophysiology of ISSHL. In our study, ISSHL occurred irrespective of age and sex, even in very young patients. We find acquired circulatory disturbances preceding ISSHL unlikely in this patient category. Despite an extensive search for the presence of a coagulopathy, an

auto-immune or other systemic illness in ISSHL, these could not be demonstrated in our patients. The unilateral occurrence of hearing loss makes a systemic pathogenesis less likely. The spontaneous occurrence of sudden hearing loss, even whilst asleep, makes a labyrinthine membrane rupture unattractive. Although no seasonal influence was demonstrated on occurrence of ISSHL, our patients were more frequently affected by an upper respiratory infection or by herpes labialis infection shortly before occurrence of ISSHL, compared to the normal population. A priming effect of a previous upper respiratory infection, leading to reactivation of a latent herpes virus infection which triggers an overwhelming inflammatory reaction in the labyrinth, damaging its delicate structures and causing hearing loss may be deduced from these findings, although the exact mechanism operational in viral reactivation and its interaction with inner ear immunity remain obscure.

Extensive virus serological monitoring and culturing revealed only scarce indications of a viral infection in ISSHL, too incoherent to establish a causal relationship with the hearing loss. A non-primary herpetic infection, as may be present in ISSHL probably does not lead to a detectable antibody titer.

In experimental herpes viral labyrinthitis, we found a synergistic effect of aciclovir and prednisolone treatment on hearing recovery and cochlear histopathology in the guinea pig inner ear. Since the experimental situation differs from clinical practice in excluding treatment delay, treatment of ISSHL might be divided in two phases. Only in the first, very early phase after ISSHL a combination therapy directed at the causative agent might be useful, combined with therapy aimed at dampening the inflammatory reaction. Most patients will present with hearing loss in a later phase and at this second phase, therapy should be directed primary towards a powerful suppression of the destructive inflammatory reaction, perhaps with an even higher corticosteroid dosage than we have used in this study. This two-phase theory in ISSHL therapy provides another argument for the commonly accepted fact that ISSHL should be regarded as an otological emergency.

Recommendations

Various therapeutic strategies have been applied in ISSHL, indicating the absence of a truly effective therapy. Our study results provide some support for earlier reports suggesting a beneficial effect on hearing recovery from the early application of corticosteroids in ISSHL. No beneficial effect from the application of aciclovir in ISSHL can be derived from this study, in contrast to our experimental findings. Based on this theoretical and experimental model of the pathophysiology of ISSHL, we propose a two-phase treatment regimen of ISSHL, which is based chiefly on the anti-inflammatory properties of corticosteroids in ISSHL in the second phase whilst only in the first, very early phase after hearing loss, therapy is directed towards the possible provoking agent by adding aciclovir.

Each new therapy of ISSHL should only be applied in an investigative setting. This makes a careful evaluation of the symptom sudden sensorineural hearing loss possible. Considerable methodological difficulties can be expected in performing such a trial, mainly due to the low incidence of ISSHL and to its high spontaneous

recovery rate. How to define recovery of ISSHL has proven to be difficult. Hearing recovery of ISSHL is certainly not equivalent to cure because often, considerable hearing damage remains. New therapeutic initiatives in ISSHL patients should be based on a thorough pathophysiological model before ISSHL patients are subjected to it. Reporting negative outcome of ISSHL therapy trials is obligatory because ISSHL patients are often exposed to therapeutic regimens lacking scientific support. Continuing a combination of research efforts aimed at the understanding of the pathophysiology of ISSHL with clinical research might provide relief to future ISSHL patients.

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Chapter 9

SUMMARY AND CONCLUSIONS

Summary

Since the beginning of the 20th century, otologists have reported cases of sudden, unexpected sensorineural hearing loss. Today, in spite of the advancements in medicine, the pathophysiology of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) has not been elucidated and little can be offered to people struck by the hearing loss.

In ISSHL, sensorineural hearing impairment or deafness develops during a very short period in otherwise healthy, and previously normally hearing persons. No population at risk can be identified. Generally, no predisposing factors are present and it is not uncommon for the hearing loss to be noticed at awakening. However, in our ISSHL patients an upper respiratory infection had been present within one month before ISSHL occurred in 30% of cases, although no seasonal influence could be established on occurrence of ISSHL.

Most cases of ISSHL are unilateral but infrequently, both ears are involved. Spontaneous hearing recovery is reported in 45-65% of cases, although in a small minority of cases hearing will recover to functional levels. Hearing recovery prognosis depends on the initial severity of the hearing loss, its prognosis being more favourable in mild to moderate initial hearing loss and worse in profound initial hearing loss. Other factors of prognostic value might be the pure-tone audiogram shape and vestibular involvement, although these could not be confirmed in our clinical study. A majority of patients suffer from tinnitus, which often persists and can be extremely discomforting. Loss of hearing is often accompanied by a pressure sensation or by a mild pain in the ear, which sometimes radiates to the mandibular or temporal regions. This sensation might intensify under the influence of stress. Many patients experience a sense of disequilibrium but some are severely disabled by rotational vertigo, making it impossible to walk straight. Vestibular complaints usually disappear within a few weeks.

The difficulties encountered in elucidating the pathophysiology of ISSHL and in designing an effective therapeutic strategy might be attributed to two factors. The first is the closed, delicate compartment formed by the inner ear, inhibiting access to study its pathophysiology. The second is the low incidence of ISSHL, which does not permit the establishment of the number of observations needed to evaluate new therapeutic modalities. All publications on ISSHL suffer from these limitations to a greater or lesser extent. Furthermore, the literature on ISSHL lacks comparability because no consensus exists on the definition of ISSHL. In this thesis, ISSHL is defined as follows:

1. Perceptive hearing loss
2. Etiology remains unknown after clinical, laboratory and imaging studies
3. Hearing loss occurred within 24 hours
4. Hearing loss is nonfluctuating
5. Severity of the hearing loss averages at least 30 dB HL for three subsequent one octave steps in frequency as shown in the standard pure-tone audiogram
6. Blank otological history.

Our definition of ISSHL closely matches the diagnostic criteria used by the majority of ENT-surgeons in the Netherlands and in Flanders (Chapter 4). The restrictions mentioned earlier are apparent when reviewing the literature on ISSHL.

Chapter 2 reviews the literature concerning the etiology of ISSHL. The applied definition of ISSHL is verified. The following hypotheses concerning the etiology of ISSHL are postulated in the literature:

1. Disturbance of labyrinthine blood circulation
2. Subclinical viral labyrinthitis
3. Spontaneous labyrinthine membrane rupture
4. Autoimmune mediated pathogenesis

Experimental support, clinical evidence, laboratory and radiological findings and post mortem histopathological evidence categories are weighted for each etiological hypothesis. In the literature, insufficient evidence exists to assume a primary circulatory disturbance or a spontaneous labyrinthine membrane rupture to be responsible for ISSHL. An autoimmune mediated pathogenesis is an attractive explanation but lacks support. Circumstantial evidence suggests a viral infection of the labyrinth to provide an explaination for a majority of ISSHL cases. Therefore, a virally mediated pathophysiology of ISSHL is studied further in this thesis.

Chapter 3 evaluates the literature on therapeutical strategies in ISSHL. The applied definition of ISSHL is verified. Trial designs are evaluated on comparativeness and on internal and external validity. Most therapeutic regimens in ISSHL are directed towards improving a suggested impaired labyrinthine blood supply or towards attenuation of a possible labyrinthine inflammatory process. No evidence of a therapy related effect is found from either improving cochlear blood supply or from thrombolysis. Two studies indicate a limited positive effect from the early administration of steroids on hearing recovery prognosis in ISSHL. Many other therapeutical modalities have been insufficiently evaluated. We recommend ISSHL treatment to take place in a carefully designed clinical trial with emphasis on comparativeness, internal and external validity.

In Chapter 4, the results of a survey on diagnosis and treatment of ISSHL are reported, based on the opinion of 230 Dutch and 50 Flemish ENT-surgeons. Questions concern definition, incidence, diagnosis, therapy and possible etiology of ISSHL. Diagnostic criteria used to define ISSHL match our definition of ISSHL closely. The incidence of ISSHL in the Netherlands and in Flanders varies with preciseness in applying diagnostic criteria and is estimated 8/100,000 in the Netherlands and 14.6/100,000 in Flanders. Considerable differences are found in diagnostic accuracy and in therapeutic strategy in ISSHL between individual ENT-surgeons and between the Netherlands and Flanders. We recommend the use of a diagnostic protocol in ISSHL, based on a differential diagnosis, thereby preventing

diagnostic omissions. Therapy of ISSHL is considered fruitless 10 days after the hearing loss has occurred. Corticosteroids are often applied in ISSHL, but other therapeutic strategies and combinations of treatment are also used frequently. These regimens often lack a scientific basis. Treatment results are comparable to the spontaneous recovery rate reported in ISSHL. Fundamental research aimed at elucidating the pathophysiology of ISSHL might lead to further agreement on etiology and therapy of ISSHL.

Chapter 5 presents an animal model of the pathophysiology of ISSHL. Establishing an animal model of ISSHL seems obligatory, since the delicacy of the structures involved inhibits further insight in the pathophysiology of ISSHL in humans. A viral labyrinthitis has been postulated to play a role in the pathophysiology of ISSHL, based on circumstantial evidence. Experimental viral labyrinthitis elicited by various virus families leaves a virus-specific pattern of cochlear damage. Herpes viruses provide the best matching pattern in the distribution of cochlear damage when compared to ISSHL postmortem cochlear histopathology. In this study, we elicit herpetic viral labyrinthitis in guinea pigs using perilymphatic inoculation with HSV-1. A control group is inoculated with the culture medium only. Infection is confirmed by the measurement of HSV antibodies. Hearing and balance are monitored. Cochlear damage is evaluated by light and electron microscopy. In all HSV-1 inoculated animals, rapid loss of hearing occurs, but balance remains undisturbed. Seroconversion takes place, but no systemic manifestations of herpetic infection are observed. The control group demonstrates no cochleovestibular or systemic symptoms. When comparing cochlear histopathology in ISSHL to experimental viral HSV-1 labyrinthitis, strong similarities are found: degeneration of the stria vascularis, destruction of the organ of Corti, loosening of the tectorial membrane and inflammatory changes in neural structures. Based on clinical and histopathological characteristics, experimental HSV-1 labyrinthitis provides a suitable model for ISSHL. These findings provide further support for the hypothesis that viral labyrinthitis might play an important role in the pathophysiology of ISSHL. The outcome of this study provides an adequate animal model for further elucidating the pathogenesis and treatment modalities in ISSHL.

In Chapter 6, the therapeutic efficacy of aciclovir (Zovirax®) and prednisolone in experimental herpes simplex type 1 (HSV-1) viral labyrinthitis in the guinea pig is described. Experimental HSV-1 labyrinthitis provides a model for ISSHL (Chapter 5). Corticosteroids improve hearing recovery prognosis in ISSHL but the effects of aciclovir are unknown. In this experiment, we induce HSV-1 labyrinthitis in 12 guinea pigs. Three animals receive no treatment, 3 receive prednisolone, 3 receive aciclovir and 3 receive both. Hearing, HSV-1 antibody titers and cochlear pathology are evaluated. Corticosteroids are able to alleviate hearing loss and to limit cochlear damage in experimental HSV-1 labyrinthitis. Adding aciclovir to prednisolone treatment provides earlier relief of the hearing loss and further limitation of structural cochlear damage in experimental HSV-1 labyrinthitis. Our study results suggest a

synergistic therapeutical effect of the combination of corticosteroids and aciclovir in the treatment of our ISSHL model. The value of this combined treatment for ISSHL patients remains to be demonstrated.

In Chapter 7, the use of Gadolinium enhanced magnetic resonance imaging (Gd-MRI) for identification of labyrinthine pathology in ISSHL is described. To this date, the role of MRI in ISSHL has been limited to excluding underlying pathology such as cerebellopontine angle lesions. Gd-MRI is able to detect the presence of a subclinical labyrinthitis in ISSHL. Its sensitivity in daily clinical practice is unknown. We describe Gd-MRI findings in 27 ISSHL patients taking part in a prospective multicenter clinical trial. MRI findings are related to the severity of the hearing loss, to vestibular involvement and to the time interval between occurrence of ISSHL and imaging. Pathological enhancement of the cochlea indicating a labyrinthitis is found in one case of ISSHL. In 26 cases, no pathological enhancement can be established. Study results indicate that magnetic resonance imaging in ISSHL is valuable for excluding cerebellopontine angle lesions which present as sudden sensorineural hearing loss. In daily clinical practice, its sensitivity for identification of an intralabyrinthine or neural inflammatory process in ISSHL is low. Such a process might only be observed during the very early phase following the occurrence of ISSHL and might be attenuated by anti-inflammatory therapy. Therefore, an imaging protocol is recommended in which at least unenhanced T1- and gadolinium enhanced T1 weighted MR images are acquired as early as possible in ISSHL, preferably before treatment is started. This makes ISSHL not only a neuro-otological but also a neuro-radiological emergency.

Chapter 8 describes the therapeutic value of the antiviral drug aciclovir (Zovirax®) on hearing recovery in 44 ISSHL patients receiving prednisolone as evaluated in a multicenter clinical trial. The study is designed prospectively, randomized, double-blind and placebo-controlled. Subjective parameters include hearing recovery, tinnitus, a pressure sensation on the affected ear and disequilibrium or vertigo. Audiometric parameters include pure-tone and speech audiometry. A 1 year follow-up is obtained. Tinnitus, occurring in a majority of patients, has a poor prognosis. Both the pressure-sensation and disequilibrium or vertigo have a favourable prognosis. Hearing recovery prognosis depends on the severity of initial hearing loss, and not on vestibular involvement. No beneficial effect from combining aciclovir with prednisolone on hearing recovery prognosis in ISSHL can be established, in contrast to our experimental findings (Chapter 6). Study results confirm earlier reports of a mild beneficial effect on hearing recovery prognosis from the early application of corticosteroids. Treatment aimed at the possible etiological agent might be benificial only in the very early phase of the hearing loss. However, no truly successful therapy can be offered to the ISSHL patient, because often, considerable hearing impairment remains.

Conclusions

1. ISSHL is a disabling disease.

2. The incidence of ISSHL implies that a considerable number of patients suffer from ISSHL annually.

3. A diagnostic protocol should be used when evaluating sudden sensorineural hearing loss. This prevents diagnostic omissions.

4. ISSHL should be treated within a multicenter clinical trial.

5. A subclinical viral labyrinthitis seems to play an important role in the pathophysiology of ISSHL.

6. Herpes simplex virus type 1 labyrinthitis provides strong histopathological correlations with ISSHL.

7. A synergistic therapeutical effect exists from combined treatment with anti-inflammatory and antiviral medication on hearing recovery and histopathological cochlear damage in experimental herpes simplex type 1 viral labyrinthitis.

8. ISSHL is both a neuro-radiological emergency and a neuro-otological emergency. A labyrinthitis can probably only be visualized on gadolinium enhanced MRI during the very early phase of hearing loss.

9. Corticosteroids provide a limited beneficial effect on hearing recovery in ISSHL. This effect might be due to a limitation of cochlear damage by the attenuation of the cochlear inflammatory response.

10. In our study design, intravenous aciclovir treatement of ISSHL has not been proven clinically beneficial. Theoretically and experimentally, this benificial effect exists only in the very early phase after occurrence of ISSHL.

SAMENVATTING

Samenvatting

Sinds het begin van deze eeuw zijn beschrijvingen bekend van ogenschijnlijk gezonde en normaal horende personen die plotseling slechthorend of doof worden. Ondanks de enorme vooruitgang in de medische wetenschap is dit ziektebeeld tot nu toe onbegrepen. In de meeste gevallen kan geen relatie tussen het plotselinge perceptieve gehoorverlies en een onderliggend ziektebeeld worden gelegd en spreekt men van idiopathisch plotseling perceptief gehoorverlies (Eng: Idiopathic Sudden Sensorineural Hearing Loss, ISSHL). De pathofysiologie van ISSHL blijft tot op heden onopgehelderd en een doeltreffende behandeling ontbreekt.
Er bestaat geen populatie met een verhoogde kans op het ontwikkelen van ISSHL. Omstandigheden waardoor het gehoorverlies zou kunnen worden geluxeerd zijn erg moeilijk aan te geven: het gehoorverlies wordt niet zelden bij het opstaan bemerkt. In onze patiëntenpopulatie deed zich bij 30% van de gevallen een bovenste luchtweginfectie in de maand voorafgaande aan het gehoorverlies voor, hoewel het ontstaan van ISSHL niet seizoengebonden blijkt te zijn.
Meestal treedt het gehoorverlies enkelzijdig op, incidenteel zijn beide oren aangedaan. Spontaan herstel van het gehoor wordt beschreven in 45-65% van de gevallen, alhoewel in een minderheid van de patiënten een functioneel rest-gehoor overblijft. Herstel van het gehoor is afhankelijk van de ernst van het initiële gehoorverlies: is dit zeer ernstig, dan is de prognose somber, is dit mild of matig dan is de prognose minder ongunstig. Mogelijke andere prognostische factoren zijn betrokkenheid van het evenwichtsorgaan bij het gehoorverlies en de vorm van het audiogram, alhoewel deze laatste factoren niet door ons onderzoek konden worden bevestigd. Vrijwel alle patiënten klagen over oorsuizen. Het persisteren van dit oorsuizen blijkt op de langere termijn naast het slechte gehoor één van de grootste problemen na ISSHL te vormen. Doorgaans voelt men een wat drukkend of pijnlijk gevoel rond en in het oor hetgeen soms rond het oor uitstraalt. Bij enkele patiënten persisteert deze sensatie en neemt zij toe onder invloed van inspanning of stress. Het ontstaan van het gehoorverlies gaat vaak gepaard met evenwichtsstoornissen, variërend van een licht gevoel in het hoofd tot een heftige draaisensatie waarbij het onmogelijk is recht te lopen. De prognose van deze evenwichtsstoornissen is in het algemeen op korte termijn gunstig.
Twee eigenschappen van ISSHL bemoeilijken het onderzoek naar de ontstaanswijze en behandeling. Ten eerste is het binnenoor zeer kwetsbaar en daardoor moeilijk toegankelijk voor onderzoek. Ten tweede is, gezien het percentage spontaan herstel, een grote serie waarnemingen nodig om conclusies te kunnen verbinden aan empirisch onderzoek. Hiervoor komt het ziektebeeld niet vaak genoeg voor.
Literatuuronderzoek naar idiopathisch plotseling perceptief gehoorverlies wordt bovendien bemoeilijkt door het ontbreken van een eensluidende definitie. In dit proefschrift wordt de volgende definitie voorgesteld:

1. Perceptief gehoorverlies
2. Oorzaak gehoorverlies kan niet worden geïdentificeerd na klinisch, beeldvormend en laboratoriumonderzoek.
3. Gehoorverlies is opgetreden binnen 24 uur
4. Gehoorverlies fluctueert niet
5. Ernst gehoorverlies is gemiddeld tenminste 30 dB HL voor 3 of meer octaafstappen in het standaard toondrempel audiogram
6. Blanco otologische voorgeschiedenis.

Deze definitie van ISSHL vertoont sterke overeenkomsten met diagnostische criteria die worden toegepast door een meerderheid van de KNO-artsen in Nederland en Vlaanderen (hoofdstuk 4).
De genoemde beperkingen komen naar voren in het literatuuroverzicht over de etiologie van ISSHL (hoofdstuk 2) en de behandeling van ISSHL (hoofdstuk 3).

In hoofdstuk 2 wordt de mogelijke etiologie van ISSHL besproken. Een viertal hypotheses met betrekking tot de pathofysiologie van idiopathisch plotseling perceptief gehoorverlies worden in de literatuur genoemd:

1. Labyrinthaire doorbloedingsstoornis
2. Subklinische virale labyrinthitis
3. Spontane labyrinthaire membraanruptuur
4. Autoimmuun labyrinthitis

Deze veronderstellingen worden -in meerdere of in mindere mate- ondersteund door een vijftal bewijscategorieën: klinische gegevens, bevindingen bij laboratorium- en bij beeldvormend onderzoek, post mortem histopathologie en dierexperimentele studies. Deze bewijscategorieën worden voor iedere etiologische hypothese beoordeeld, waarbij de gehanteerde definitie van ISSHL wordt meegewogen. Geconcludeerd wordt dat onvoldoende aanknopingspunten bestaan om de primaire labyrinthaire doorbloedingsstoornis of de spontane labyrinthaire membraanruptuur verantwoordelijk te stellen voor ISSHL. Ook voor de autoimuun labyrinthitis worden onvoldoende aanwijzingen gevonden. Voor een subklinische virale labyrinthitis als veroorzaker van ISSHL worden veelbelovende, zij het indirecte aanwijzingen gevonden. Deze hypothese wordt in dit proefschrift nader uitgewerkt.

In hoofdstuk 3 wordt de literatuur met betrekking tot de behandeling van ISSHL geëvalueerd. De opzet van deze studies wordt beoordeeld op vergelijkbaarheid en op interne en externe validiteit. Daarbij wordt de gehanteerde definitie van ISSHL geverifieerd. Behandeling van ISSHL is veelal gericht op het optimaliseren van de mogelijk gecompromitteerde cochleaire bloeddoorstroming of op het remmen van een eventueel onderliggend ontstekingsproces. Voor behandeling van ISSHL met plasma-expanders, met vaatverwijdende middelen of met ontstolling wordt geen wetenschappelijke basis gevonden. Enkele studies wijzen op een beperkt gunstig

effect van corticosteroïdbehandeling op de prognose van ISSHL. Een restgroep van andere behandelingsvormen is nog onvoldoende grondig onderzocht. Gezien het relatief hoge percentage spontaan herstel van ISSHL vergt het aantonen van een therapeutisch effect relatief grote aantallen patiënten. De incidentie van ISSHL laat dit vaak niet toe. Daarom wordt aanbevolen behandeling van ISSHL te doen plaatsvinden in een multicentrische klinische trial.

In hoofdstuk 4 wordt beschreven hoe men in de dagelijkse Nederlandse en Vlaamse KNO-praktijk omgaat met ISSHL, aan de hand van de resultaten van een enquête onder 230 Nederlandse en 50 Vlaamse KNO-artsen. Hierin is geïnformeerd naar definitie, voorkomen, diagnose, behandeling en mogelijke ontstaanswijze van ISSHL. Diagnostische criteria voor ISSHL komen goed overeen met de door ons gehanteerde definitie van ISSHL. De incidentie van ISSHL bedraagt 8/100.000 in Nederland en 14,6/100.000 in Vlaanderen. Verschillen in incidentie van ISSHL lijken afhankelijk te zijn van het stringent hanteren van diagnostische criteria. Een grote variabiliteit wordt aangetroffen in diagnostiek en behandeling van ISSHL tussen individuele KNO-artsen en tussen Nederlanders en Vlamingen.
De diagnostiek bij het symptoom plotseling perceptief gehoorverlies vertoont belangrijke omissies. Hierdoor ontstaan hiaten bij het verifiëren van de differentiaal diagnose van plotseling perceptief gehoorverlies. Het verdient daarom aanbeveling de ISSHL patiënt te screenen volgens een tevoren vastgelegd protocol. Corticosteroïden worden vaak toegepast bij ISSHL, maar ook vele andere behandelingsmodaliteiten worden, soms gecombineerd, toegediend alhoewel een duidelijke wetenschappelijke of empirische basis hiervoor ontbreekt. Behandeling van ISSHL wordt 10 dagen na het ontstaan van het gehoorverlies niet langer zinvol gevonden. Het geschatte succespercentage van ISSHL behandeling komt overeen met de in de literatuur genoemde percentages spontaan herstel. Wellicht kan meer fundamenteel onderzoek naar de ontstaanswijze van ISSHL leiden tot verdere overeenstemming over etiologie en behandeling van ISSHL.

In hoofdstuk 5 wordt een proefdiermodel van de pathogenese van ISSHL ontwikkeld, teneinde het inzicht in de pathofysiologie van ISSHL te verdiepen. De mogelijkheden hiertoe zijn bij de mens zeer beperkt (hoofdstuk 7) vanwege de kwetsbaarheid van het binnenoor. Bij het ontwikkelen van een proefdiermodel van ISSHL wordt uitgegaan van een subklinische virale labyrinthitis als oorzaak voor ISSHL. Uit eerder dierexperimenteel onderzoek naar de virale labyrinthitis blijkt een specifieke affiniteit te bestaan voor verschillende cochleaire structuren door verschillende virus-families. Deze patronen van cochleaire beschadiging wordt vergeleken met gedetailleerde beschrijvingen van de histopathologie van ISSHL. Deze blijkt sterk overeen te komen met experimentele virale labyrinthitis veroorzaakt door herpes virussen. In het proefdiermodel wordt via perilymfatische inoculatie een subklinische herpes simplex type 1 (HSV-1) labyrinthitis geïnduceerd bij de cavia, terwijl een controlegroep alleen het kweekmedium ontvangt. Primaire inoculatie wordt bevestigd door het bepalen van herpes antilichamen. Controle van gehoor- en evenwichtsfunctie vindt plaats.

Cochleaire histopathologie wordt beschreven aan de hand van licht- en elektronen microscopische beelden. Bij alle met HSV-1 geïnoculeerde proefdieren treedt zeer snel na inoculatie gehoorverlies op terwijl de evenwichtsfunctie intact blijft. Behoudens seroconversie worden geen andere manifestaties van HSV-1 infectie aangetroffen. Bij de controlegroep treedt gehoorverlies noch seroconversie op. Een vergelijking van de cochleaire histopathologie van experimentele HSV-1 labyrinthitis met de histopathologie van ISSHL levert sterke overeenkomsten op: degeneratie van de stria vascularis, destructie van het orgaan van Corti, elevatie van de tectoriaal membraan en inflammatoire veranderingen in neurale cochleaire structuren. Geconcludeerd wordt dat gebaseerd op overeenkomsten in histopathologische karakteristieken en klinische eigenschappen, experimentele HSV-1 labyrinthitis een geschikt model vormt voor ISSHL.

In hoofdstuk 6 wordt de invloed van behandeling van experimentele HSV-1 labyrinthitis in de cavia met de ontstekingsremmer prednisolon en het antivirale geneesmiddel aciclovir (Zovirax®) beschreven. Experimentele HSV-1 labyrinthitis in de cavia vormt een geschikt pathofysiologisch model voor ISSHL (hoofdstuk 5). In de klinische setting verbetert het toedienen van corticosteroïden de prognose van ISSHL. De waarde van aciclovir voor de behandeling van ISSHL is onbekend. In dit experiment wordt bij 12 cavia's een virale labyrinthitis met HSV-1 geïnduceerd. Drie dieren worden niet behandeld, 3 ontvangen prednisolon, 3 ontvangen aciclovir en 3 ontvangen de combinatie aciclovir-prednisolon. De gehoorfunctie wordt gecontroleerd en herpes-antilichamen worden bepaald. Cochleaire schade wordt geïnventariseerd door middel van lichtmicroscopie. Het toedienen van corticosteroïden leidt tot herstel van de gehoorfunctie en tot beperking van cochleaire schade. Het toevoegen van aciclovir leidt tot eerder gehoorherstel en tot verdere beperking van cochleaire beschadiging, in vergelijking met corticosteroïden als monotherapie. De combinatiebehandeling lijkt derhalve een synergistisch effect te vertonen in de experimentele situatie. Aanbevolen wordt de resultaten te extrapoleren naar de klinische setting en de combinatiebehandeling prednisolon-aciclovir te toetsen bij ISSHL patiënten.

In hoofdstuk 7 wordt gepoogd de labyrinthaire pathofysiologie van ISSHL te bestuderen door middel van kernspintomografisch (MRI) onderzoek. Tot dusverre werd MRI onderzoek bij ISSHL voornamelijk toegepast om enkele meer centraal gelegen oorzaken, zoals bijvoorbeeld tumorprocessen in de cerebellopontine hoek of multiple sclerose uit te sluiten. Voor dit doel is MRI onderzoek ook bij de door ons onderzochte patiënten geschikt gebleken.
Daamaast kan Gadolinium-enhanced MRI (Gd-MRI) onderzoek een subklinische labyrinthitis bij ISSHL aantonen. De sensitiviteit van deze waarneming is echter onbekend. De resultaten van Gd-MRI onderzoek van 27 ISSHL patiënten worden beschreven. Bevindingen bij MRI onderzoek worden gerelateerd aan de ernst van het gehoorverlies, aan betrokkenheid van het evenwichtsorgaan bij de uitval van het gehoororgaan en aan het tijdsinterval tussen het ontstaan van het gehoorverlies en het

maken van de scan. In 1 geval werd intracochleair pathologische aankleuring gevonden, passend bij een labyrinthitis, in de overige gevallen trad dit niet op. Alhoewel de waarde van MRI onderzoek bij ISSHL voor het detecteren van onderliggende pathologie ook bij onze patiënten wordt bevestigd, blijkt het aantonen van een subklinische labyrinthitis met behulp van Gd-MRI moeilijk te zijn. Een dergelijke aankleuring wordt misschien alleen in de zeer vroege fase na het ontstaan van het gehoorverlies gezien en zou bij onze patiënten nog gedempt kunnen worden door de reeds ingestelde ontstekingsremmende behandeling. Aanbevelingen worden geformuleerd voor het onderzoeken van ISSHL patiënten met behulp van MRI. Geadviseerd wordt tenminste T1 gewogen opnamen voor en na toediening van gadolinium contrast te maken. Daarnaast wordt geadviseerd om het tijdsinterval tussen gehoorverlies en MRI zo kort mogelijk te doen zijn omdat anders het lange tijdsinterval en de reeds ingestelde behandeling de labyrinthitis moeilijk detecteerbaar maken. Dit maakt ISSHL behalve tot een otologisch spoedgeval ook een radiodiagnostisch spoedgeval.

In hoofdstuk 8 worden de resultaten van een prospectief, dubbelblind, gerandomiseerd onderzoek naar de toepassing van aciclovir versus placebo naast prednisolon bij ISSHL beschreven. In een multicentrische klinische trial worden 44 ISSHL patiënten behandeld met prednisolon, waarvan 22 patiënten aciclovir ontvangen en 22 placebo. Als subjectieve uitkomstvariabelen worden herstel van het gehoor, oorsuizen, een drukgevoel op het oor en evenwichtsstoornissen door patiënten gecategoriseerd. Als audiometrische uitkomstvariabelen worden toondrempel- en spraakaudiometrie bepaald. De follow-up bedraagt een jaar. Een meerderheid van de behandelde patiënten ervaart subjectief gehoorverbetering, welke overeenkomt met gemeten verbeteringen in het toondrempelaudiogram. Tinnitus treedt frequent op na ISSHL en heeft een matige prognose. De prognose van drukgevoelens op het oor en van evenwichtsstoornissen zijn goed. Patiënten met een zeer ernstig initieel gehoorverlies hebben een slechtere prognose met betrekking tot gehoorherstel in vergelijking met patiënten met een mild of matig ernstig initieel gehoorverlies. Betrokkenheid van het evenwichtsorgaan bij het gehoorverlies blijkt niet van invloed te zijn op het gehoorherstel. Behandeling met aciclovir naast prednisolon heeft geen gunstige invloed op het gehoorherstel na ISSHL, in tegenstelling tot onze bevindingen bij experimenteel onderzoek (hoofdstuk 6). Eerdere rapportages van een beperkt gunstig effect op het gehoorherstel door het toepassen van corticosteroïden worden in dit onderzoek bevestigd. Wellicht is behandeling tevens gericht tegen het mogelijk veroorzakende agens alleen zinvol is in de zeer vroege fase nadat gehoorverlies is opgetreden.

Conclusies

1. ISSHL is een invaliderende ziekte.

2. De incidentie van ISSHL impliceert dat een aanzienlijk aantal patiënten jaarlijks door dit ziektebeeld worden getroffen.

3. Een diagnostisch protocol dient bij het symptoom plotseling perceptief gehoorverlies te worden toegepast. Dit voorkomt diagnostische omissies.

4. ISSHL dient bij voorkeur te worden behandeld in een multicentrische klinische trial.

5. Een subklinische virale labyrinthitis lijkt een belangrijke rol te spelen in de pathofysiologie van ISSHL.

6. Herpes simplex virus type 1 labyrinthitis vertoont sterke klinische en histopathologische overeenkomsten met ISSHL.

7. Een combinatiebehandeling bestaande uit anti-inflammatoire en antivirale medicamenten vertoont een synergistisch therapeutisch effect op het gehoorherstel en op de histopathologische cochleaire beschadiging in experimentele herpes simplex type 1 virale labyrinthitis.

8. ISSHL is een neuroradiologisch spoedgeval, naast een neuro-otologisch spoedgeval. Een labyrinthitis kan waarschijnlijk alleen in een zeer vroege fase na het gehoorverlies worden gezien op gadolinium enhanced MRI.

9. Corticosteroïden hebben een gunstig effect op het gehoorherstel na ISSHL. Dit effect kan wellicht worden verklaard door een beperking van cochleaire schade door remming van de cochleaire ontstekingsreactie.

10. Intraveneuze aciclovir behandeling van ISSHL levert in ons onderzoek geen klinische voordelen op. Theoretisch en experimenteel bestaat dit voordeel alleen indien toegepast in de zeer vroege fase nadat het gehoorverlies is ontstaan.

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CURRICULUM VITAE

Robert Jan Stokroos was born on March 13th, 1967 in Veendam, the Netherlands, where he graduated the Rijksscholengemeenschap Winkler Prins (Atheneum β) in 1985. He studied medicine from 1985 to 1992, when he qualified as a medical doctor (Cum Laude). Extracurricular activities included training in tropical medicine on the Akwapim ridge, Ghana, under guidance of Dr. B.E.A. Neequaye. Research efforts were made in reconstructive surgery and in experimental surgery.
From February 1992 to February 1997 he specialized in Otorhinolaryngology at the University Hospital Groningen, where he is currently employed (Head: Prof. Dr. F.W.J. Albers). In August 1993, research described in this thesis was incepted. From December 1997, he will be practicing ENT-surgery with some emphasis on otology at the University Hospital Maastricht. He is married to Rosina van der Holst, and has a son, Jasper.